Hypertension

ORIGINAL ARTICLE

Angiotensin Receptor Blockers Are Associated With a Lower Risk of Progression From Mild Cognitive Impairment to Dementia

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BACKGROUND: Previous studies found that antihypertensive medications (AHMs) acting on the renin-angiotensin system had the potential to reduce the progression from mild cognitive impairment to dementia. However, it remains unclear whether this association differs between ACE (angiotensin-converting enzyme) inhibitors and angiotensin receptor blockers.

METHODS: We conducted a retrospective cohort study in the Alzheimer's Disease Neuroimaging Initiative among 403 participants with hypertension and mild cognitive impairment at baseline. Information on AHMs received during the follow-up period, including angiotensin receptor blockers, ACE inhibitors, beta-blockers, calcium channel blockers, and diuretics, were self-reported. Cox proportional hazards models adjusted for potential confounders were used in the time to event analysis with progression to dementia as outcome.

RESULTS: Of the 403 participants, the mean (SD) age was 74.0 (7.3) years, 152 (37.7%) were female, 158 (39.2%) progressed to dementia over a median follow-up time of 3.0 years. Angiotensin receptor blockers were associated with a lower risk of progression to dementia as compared to ACE inhibitors (adjusted hazard ratio=0.45 [95% CI, 0.25–0.81]; *P*=0.023), other classes of AHMs (beta-blockers, calcium channel blockers, diuretics; adjusted hazard ratio, 0.49 [95% CI, 0.27–0.89]; *P*=0.037), and none of AHMs (adjusted hazard ratio, 0.31 [95% CI, 0.16–0.58]; *P*=0.001).

CONCLUSIONS: In patients with hypertension and mild cognitive impairment, angiotensin receptor blockers were associated with a lower risk of progression to dementia compared with ACE inhibitors and other classes of AHMs. Our findings may have important implications for clinical practice but still warrant further investigations in larger prospective cohorts or clinical trials. (***Hypertension*. 2022;79:00–00. DOI: 10.1161/HYPERTENSIONAHA.122.19378.**) • **Supplemental Material**

Key Words: angiotensin-converting enzyme inhibitors ■ angiotensin receptor blockers ■ dementia ■ mild cognitive impairment ■ progression

Individuals with mild cognitive impairment (MCI), defined by an impaired cognitive function that does not meet the criteria of dementia, bear a high risk of dementia.[1] Given the failure of trials aiming to treat dementia,[2] MCI has received considerable attention in clinical practice and research settings. MCI and hypertension are both prevalent in the elderly,[1,3] while hypertension is deleterious to cognitive function.[4] For patients with MCI and hypertension, it is important to identify the optimal antihypertensive medications (AHMs) to prevent progression to dementia.

Previous studies found that in patients who had MCI and received AHMs, those receiving AHMs acting on the renin-angiotensin system (RAS), including ACE (angiotensin-converting enzyme) inhibitors and angiotensin receptor blockers (ARBs), were less likely to progress to Alzheimer's Disease (AD) and had fewer neurofibrillary tangles in the brain, than those who did not.[5,6] ACE

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ORIGINAL ARTICLE

NOVELTY AND RELEVANCE

What Is New?

This retrospective cohort study first demonstrated that angiotensin receptor blockers were associated with a lower risk of progression from mild cognitive impairment (MCI) to dementia in patients with hypertension and MCI, compared with ACE (angiotensin-converting enzyme) inhibitors and other classes of antihypertensive medications.

What Is Relevant?

Hypertension and MCI are both prevalent in the elderly, while hypertension is deleterious to cognitive function. It is important to clarify the optimal antihypertensive medications for individuals with hypertension and MCI to prevent progression to dementia.

Clinical/Pathophysiological Implications?

In patients with hypertension and MCI, angiotensin receptor blockers were associated with a lower risk of progression to dementia compared with ACEIs and other classes of antihypertensive medications.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
AD	Alzheimer's Disease
ADAS	Alzheimer's Disease Assessment Scale-Cognitive subscale test
ADNI	Alzheimer's Disease Neuroimaging Initiative
AHM	antihypertensive medication
ARB	angiotensin receptor blocker
AT1R	angiotensin II type-1 receptor
AT2R	angiotensin II type-2 receptor
AT4R	angiotensin IV type-4 receptor
BP	blood pressure
CDR	Clinical Dementia Rating
CDR-SB	the Sum of Boxes of Clinical Dementia Rating scale
CSF	cerebrospinal fluid
MCI	mild cognitive impairment
MMSE	the Mini-Mental State Examination
RAS	renin-angiotensin system
RAVLT	Rey Auditory Verbal Learning Test

inhibitors and ARBs are first-line treatments for hypertension, and they both act on the RAS, with ARBs taking effect via the AT1Rs (angiotensin II type-1 receptors) and ACE inhibitors acting upstream at the ACE.[7] The angiotensin hypothesis has recently been proposed that the RAS plays a role in brain function.[8,9] Angiotensin II and IV seem to be neuroprotective through AT2Rs (angiotensin II type-2 receptors) and AT4Rs (angiotensin IV type-4 receptors).[8–11] Medications that increase angiotensin-mediated activity at the AT2Rs and AT4Rs (eg, ARBs) may provide better brain protection compared with those decreasing activity at these receptors (eg, ACE inhibitors).[12] A previous large cohort study showed that ARBs were associated with a lower incidence of dementia compared with ACE inhibitors or other cardiovascular drugs in a predominantly male population.[13] Recent studies also recognized that ARBs were associated with less amyloid-β (Aβ) deposition and tau protein,[14,15] less brain atrophy,[16,17] and slower cognitive decline.[17–19] However, it remains unclear whether and to what extent ARBs are superior to ACE inhibitors in reducing progression to dementia in patients with MCI.

Therefore, we conducted this retrospective cohort study to investigate whether ARBs are associated with a lower risk of progression to dementia in patients with hypertension and MCI, compared with ACE inhibitors and other classes of AHMs.

METHODS

Study Sample

All data used in this study are available to eligible researchers after registration and can be accessed at the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI is to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org. Written informed consent was obtained for all participants, and study procedures were approved by the institutional review board at each participating center. The data used in this study were downloaded from the ADNI data repository on May 1, 2021.

Inclusion criteria relevant to our analysis were as follows: diagnosis of MCI; at least 2 or more visits after MCI diagnosis; presence of hypertension, defined as self-reported history of hypertension, any use of AHMs, or the mean systolic blood pressure (BP) ≥140 mm Hg or diastolic BP ≥90 mm Hg during the follow-up period. We excluded those without baseline cerebrospinal fluid (CSF) biomarker results or with insufficient or inconsistent data on sociodemographic characteristics and cognitive status.

Assessments

Demographic and clinical characteristics were collected at baseline. For BP, we calculated the mean value during the follow-up period, which reflected the BP control level of each participant during the follow-up period. AD medications included donepezil, tacrine, rivastigmine, memantine, and galantamine.

Participants were reassessed every 6 months or annually for progression from MCI to dementia (AD or other types), or nonprogression, which was defined as stable MCI or reversion to normal cognition. Diagnostic procedures have been reported in detail previously.[20] Scores on the Mini-Mental State Examination (MMSE), the Clinical Dementia Rating (CDR) scale, the Sum of Boxes of CDR (CDR-SB), the Alzheimer's Disease Assessment Scale-Cognitive subscale test (ADAS-Cog-13), and the Rey Auditory Verbal Learning Test (sum of trials 1–5) were assessed at baseline and reassessed at every visit. A lower score on the MMSE or Rey Auditory Verbal Learning Test means worse cognition, while a higher score on the CDR, CDR-SB, or ADAS-Cog-13 means worse cognition.[20]

AHMs Classification and Groups Design

AHMs information was self-reported by participants at every visit during the follow-up period and was classified into 5 groups: ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, and diuretics. To maintain an adequate sample size for analysis, multiple AHMs use was allowed because most participants received combined therapy in our study.

According to the classes of AHMs received during the follow-up period, participants were initially classified into 2 groups with and without AHMs: the hypertension-antihypertensives group and the hypertension-no antihypertensives group. Then, the hypertension-antihypertensives group was divided into 2 groups: participants whose AHMs included RAS-acting medications (hypertension-RAS), and the remaining participants who received AHMs of other classes including beta-blockers, calcium channel blockers, or diuretics (hypertension-other antihypertensives). Finally, the hypertension-RAS group was subdivided into 2 groups: participants whose AHMs included ARBs but not ACE inhibitors (hypertension-ARB), and participants whose AHMs included ACE inhibitors but not ARBs (hypertension-ACE inhibitor), excluding those whose AHMs involved both of ACE inhibitors and ARBs during the follow-up period.

Statistical Analysis

Baseline characteristics were compared across different AHMs groups using univariate ANOVA or Kruskal-Wallis test for continuous variables, and χ^2 or Fisher exact test for categorical variables.

Kaplan-Meier survival analyses and Cox proportional hazards models were used to determine the association of different AHMs groups with the risk of progression to dementia. Time to event is expressed as years from baseline to progression to dementia or participants' last visit in the absence of progression (ie, censored data). The multivariable adjustment was performed using variables that had a significant univariate association ($P<0.1$) or were known to be associated with progression from MCI to dementia, including age, sex, race, education length, ever alcohol abuse, ever smoker, family history of dementia, hyperlipidemia, coronary heart disease, atrial fibrillation, transient ischemic attack or stroke, diabetes, chronic kidney disease, antiplatelet agents, AD medications use, Apolipoprotein E (Apo E) status, body mass index (BMI), systolic BP, diastolic BP, baseline levels of amyloid-$\beta_{1\text{-}42}$ ($A\beta_{1\text{-}42}$), total tau (t-tau), and tau phosphorylated at threonine 181 (p-tau_{181}) in CSF, and scores on MMSE and CDR-SB at baseline. The proportional hazards assumption was assessed using the Schoenfeld residual test. For adjustment variables for which the proportional hazards assumption did not hold, we included the time-interaction term or stratification variable in the multivariable model to deal with nonproportionality.

Additionally, we conducted several sensitivity analyses to assess the robustness of our results. First, we used the Fine-Gray methods accounting for death as a competing risk in the models. Second, we excluded participants who did not report the history of hypertension and were normotensive during the follow-up period, because these participants might take AHMs for other indications (eg, diabetes). Finally, we performed 1-year lag analysis by further excluding participants with follow-up time or progression to dementia <1 year from the baseline to avoid recall bias as possible.

Linear mixed-effects models were used to estimate the longitudinal change of scores on MMSE, CDR-SB, ADAS-Cog-13, and Rey Auditory Verbal Learning Test from baseline of different groups using follow-up time (years) as the time variable. All Linear mixed-effects models included a group*time interaction item with random intercepts and slopes (ie, time in years), and the baseline score of the corresponding cognitive test as a fixed effect, and were adjusted for potential confounders mentioned above. We visualized the results of linear mixed-effects models using the method of marginal effect over the levels of factors.

Two-sided $P<0.05$ were considered statistically significant. P were corrected using Benjamini & Hochberg method when involving multiple comparisons for groups. All statistical analyses were performed using the R statistical software (version 4.0.3).

RESULTS

Participants

A total of 403 participants with hypertension and MCI at baseline were included in our analysis (Figure 1). Of them, the mean (SD) age was 74.0 (7.3) years, 152 (37.7%) were female, 158 (39.2%) progressed to dementia over a median (interquartile range) follow-up time of 3.0 (2.0–5.0) years, and the 3-year progression-free survival rate was 67.0% (95% CI, 62.2–72.0). Progression rates for different AHMs groups were summarized in Table S1. Except for 13 participants whose AHMs involved both of ACE inhibitors and ARBs during the follow-up period, baseline characteristics for the remaining 390 participants, categorized into the different AHMs groups, were summarized in Table 1. Participants in the hypertension-ARB group were more likely to be ever smokers, had a higher prevalence of hyperlipidemia and diabetes, but a lower prevalence of coronary heart disease, were less likely to be Apo E4 allele carriers, and tended to have a higher BMI and a lower CSF t-tau level.

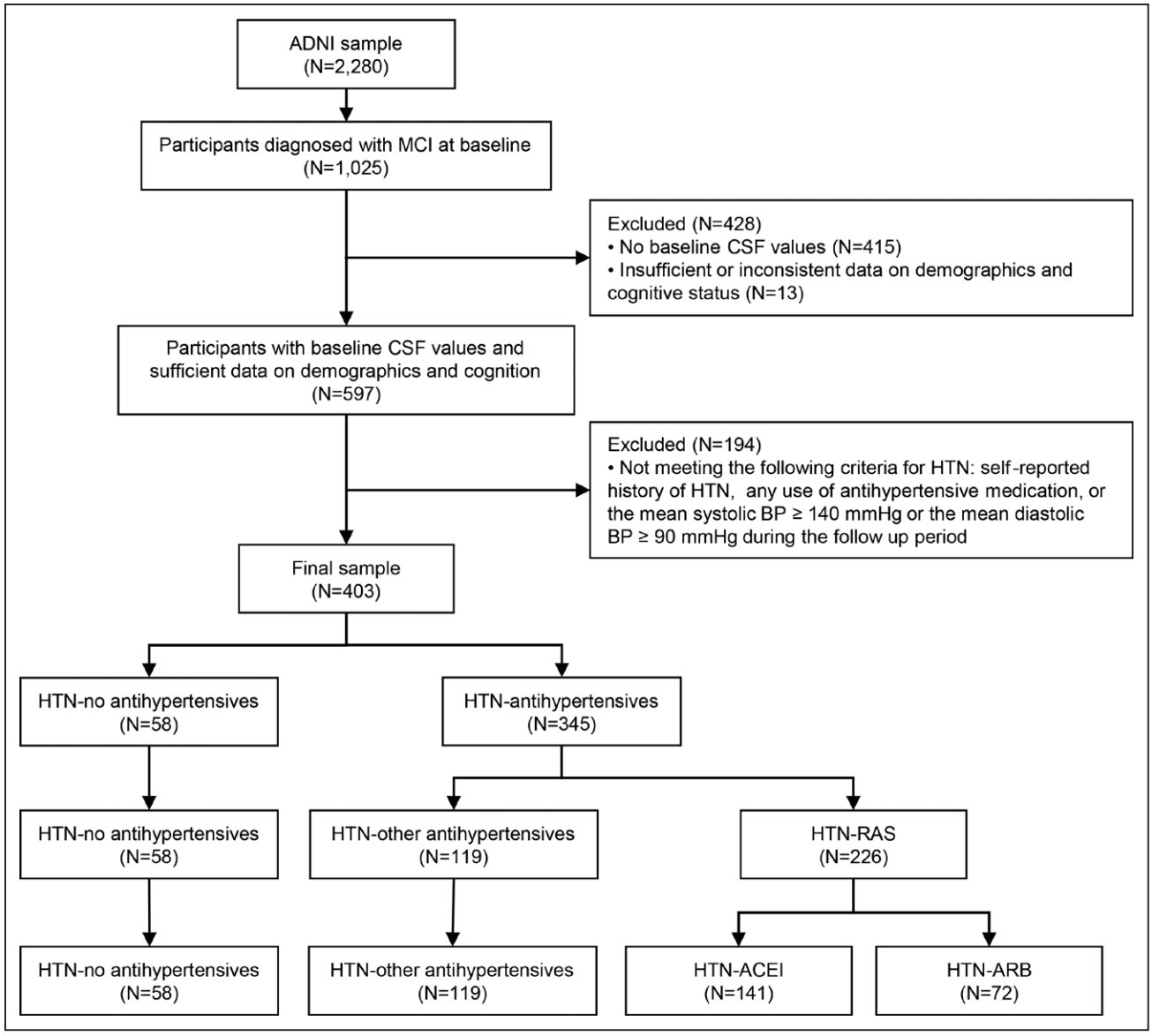

Figure 1. Flowchart of participants included in this study.
ACEI indicates angiotensin-converting enzyme inhibitor; ADNI, Alzheimer's Disease Neuroimaging Initiative; ARB, angiotensin receptor blocker; BP, blood pressure; CSF, cerebrospinal fluid; HTN, hypertension; MCI, mild cognitive impairment; and RAS, renin-angiotensin system.

Kaplan-Meier Analysis

First, the 3-year progression-free survival rate was higher in the hypertension-antihypertensives group (71.0% [95% CI, 66.2–76.3]), compared with the hypertension-no antihypertensives group (41.6% [95% CI, 29.8–58.1]; log-rank $P<0.001$; Figure 2A). Second, compared with hypertension-no antihypertensives group, the 3-year progression-free survival rate was higher in the hypertension-RAS group (73.8% [95% CI, 68.0–80.1]; log-rank $P<0.001$), and the hypertension-other antihypertensives group (65.8% [95% CI, 57.3–75.5]; log-rank $P=0.001$). But there was no significant difference between the hypertension-RAS group and the hypertension-other antihypertensives group (log-rank $P=0.100$; Figure 2B). Finally, the 3-year progression-free survival rate was higher in the hypertension-ARB group (80.9% [95% CI, 72.0–90.8]), compared with the hypertension-ACE inhibitor group (67.1% [95% CI, 59.2–76.0]; log-rank $P=0.025$), hypertension-other antihypertensives group (log-rank $P=0.025$), and hypertension-no antihypertensives group (log-rank $P<0.001$). But there was no significant difference between the hypertension-ACE inhibitor group and the hypertension-other antihypertensives group (log-rank $P=0.800$; Figure 2C).

Cox Regression According to Different AHMs Groups

The univariate models presented similar results to the Kaplan-Meier analysis (Table 2; Table S2). In the multivariate models, hypertension-ARB group had a lower

Table 1. Baseline Characteristics of Participants With Hypertension and Mild Cognitive Impairment at Baseline According to Different Antihypertensive Medication Groups (N=390)

Characteristics	HTN-no antihypertensives	HTN-antihypertensives			*P* value
		HTN-other antihypertensives	HTN-ACEI	HTN-ARB	
n	58	119	141	72	
Follow up, mo	24.00 (12.00–36.00)	36.00 (21.00–60.00)	36.00 (24.00–60.00)	48.00 (36.00–72.00)	-
Age, y	74.59 (6.90)	74.27 (7.61)	74.06 (7.32)	73.14 (6.99)	0.672
Female (%)	20 (34.5)	50 (42.0)	47 (33.3)	32 (44.4)	0.298
Race, %					0.149
White	56 (96.6)	112 (94.1)	133 (94.3)	60 (83.3)	
Asian	1 (1.7)	2 (1.7)	2 (1.4)	4 (5.6)	
Black	1 (1.7)	3 (2.5)	2 (1.4)	5 (6.9)	
Other or unknown	0 (0.0)	2 (1.7)	4 (2.8)	3 (4.2)	
Education length, y	16.00 (14.00–18.00)	16.00 (14.00–18.00)	16.00 (14.00–18.00)	16.00 (14.00–18.00)	0.915
aMCI (%)	58 (100.0)	118 (99.2)	141 (100.0)	71 (98.6)	0.501
Family history of dementia (%)	36 (62.1)	77 (64.7)	76 (53.9)	43 (59.7)	0.343
Ever alcohol abuse (%)	2 (3.4)	5 (4.2)	9 (6.4)	3 (4.2)	0.767
Ever smoker (%)	22 (37.9)	47 (39.5)	53 (37.6)	38 (52.8)	0.162
Hyperlipidemia (%)	25 (43.1)	73 (61.3)	85 (60.3)	48 (66.7)	0.042
Coronary heart disease (%)	2 (3.4)	21 (17.6)	33 (23.4)	9 (12.5)	0.005
Atrial fibrillation (%)	0 (0.0)	5 (4.2)	2 (1.4)	3 (4.2)	0.232
TIA or stroke (%)	1 (1.7)	7 (5.9)	10 (7.1)	5 (6.9)	0.508
Diabetes, %	1 (1.7)	10 (8.4)	28 (19.9)	11 (15.3)	0.002
Chronic kidney disease, %	0 (0.0)	2 (1.7)	4 (2.8)	5 (6.9)	0.082
Antiplatelet agents, %	34 (58.6)	79 (66.4)	107 (75.9)	49 (68.1)	0.091
AD medication use, %	32 (55.2)	64 (53.8)	62 (44.0)	38 (52.8)	0.313
Multiple AHMs use, %	-	-	99 (70.2)	53 (73.6)	-
Apo E status, %					0.307
No E4 allele	24 (41.4)	58 (48.7)	78 (55.3)	43 (59.7)	
1 E4 allele	24 (41.4)	48 (40.3)	51 (36.2)	23 (31.9)	
2 E4 alleles	10 (17.2)	13 (10.9)	12 (8.5)	6 (8.3)	
BMI, kg/m^2	26.50 (4.60)	27.21 (5.24)	27.66 (4.61)	28.94 (5.23)	0.030
Systolic BP, mm Hg*	146.06 (9.46)	133.45 (11.36)	137.46 (13.20)	137.74 (12.55)	<0.001
Diastolic BP, mm Hg*	76.84 (6.59)	72.81 (6.93)	73.22 (7.64)	75.88 (8.06)	0.001
A$\beta_{1\text{-}42}$, pg/mL	148.00 (124.00–181.50)	150.00 (129.00–202.00)	156.00 (134.00–222.00)	167.50 (133.50–216.00)	0.106
T-tau, pg/mL	82.25 (56.62–120.50)	83.20 (58.00–122.00)	75.30 (51.20–110.00)	62.35 (43.35–96.70)	0.020
P-tau$_{181}$, pg/mL	40.25 (23.05–60.08)	36.50 (24.60–51.30)	34.80 (22.00–46.40)	28.55 (20.60–43.07)	0.125
CDR	0.50 (0.00)	0.50 (0.00)	0.50 (0.00)	0.50 (0.00)	-
CDR-SB	1.50 (1.00–2.00)	1.50 (1.00–2.00)	1.00 (1.00–2.00)	1.00 (0.50–1.62)	0.198
MMSE	27.05 (1.89)	27.64 (1.77)	27.55 (1.88)	27.94 (1.79)	0.051
ADAS-Cog-13	17.03 (6.81)	16.40 (7.01)	16.65 (6.84)	15.57 (6.70)	0.630
RAVLT	34.22 (10.26)	33.89 (10.15)	33.04 (10.45)	34.25 (10.18)	0.807

Data are presented as means (SD), medians (interquartile range), or numbers (%). ACEI indicates angiotensin-converting enzyme inhibitor; AD, Alzheimer's disease; ADAS-Cog-13, the Alzheimer's Disease Assessment Scale-Cognitive subscale test; AHM, antihypertensive medication; aMCI, amnestic mild cognitive impairment; ARB, angiotensin receptor blocker; Aβ1-42, amyloid beta 1-42; BMI, body mass index; BP, blood pressure; CDR, the Clinical Dementia Rating scale; CDR-SB, the Sum of Boxes of the Clinical Dementia Rating scale; HTN, hypertension; MMSE, the Mini Mental State Examination; P-tau181, tau phosphorylated at threonine 181; RAVLT, the Rey Auditory Verbal Learning Test.; T-tau, total tau; and TIA, transient ischemic attack.

*Blood pressure was the mean value during the follow-up period.

risk of progression of MCI to dementia compared with hypertension-no antihypertensives group (adjusted-HR, 0.31 [95% CI, 0.16–0.58]; *P*=0.001), hypertension-other antihypertensives (adjusted-HR, 0.49 [95% CI, 0.27–0.89]; *P*=0.037), and hypertension-ACE inhibitor group (adjusted-HR, 0.45 [95% CI, 0.25–0.81]s; *P*=0.023). No significant differences were observed between the other groups in the multivariate models

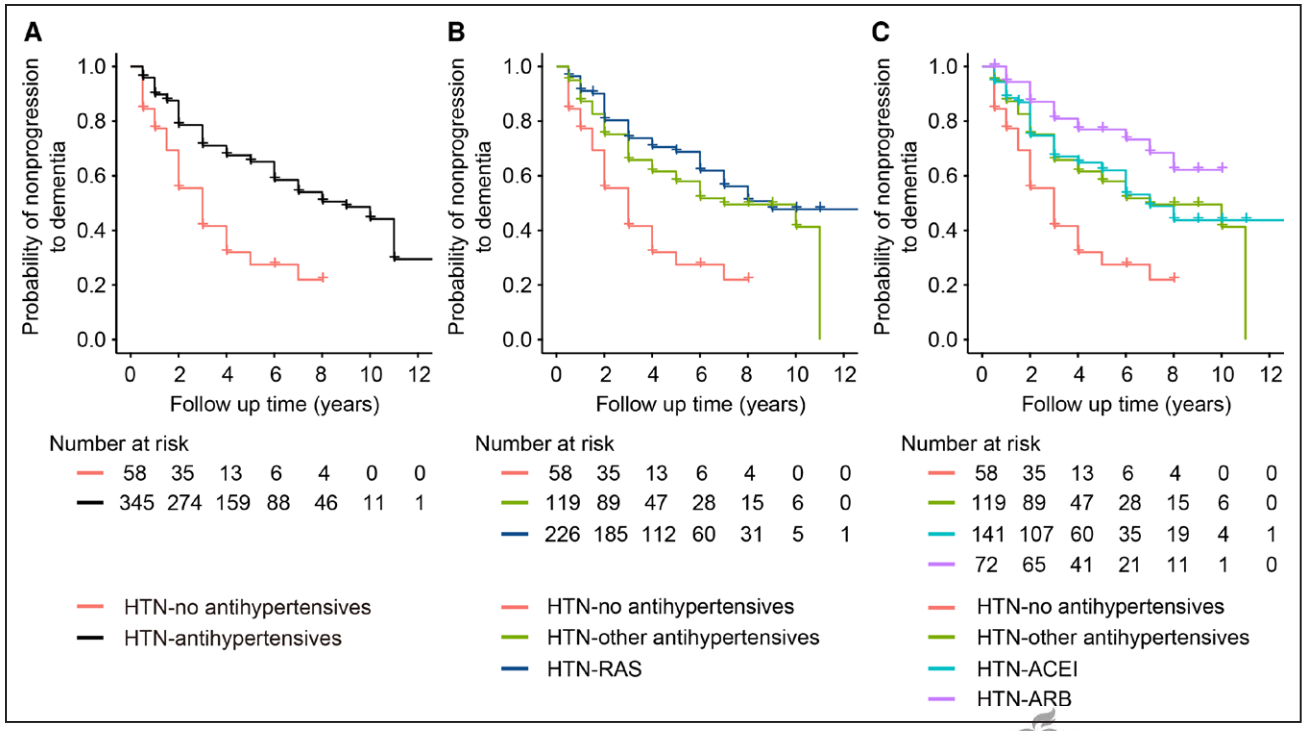

Figure 2. Kaplan-Meier survival analyses for progression from mild cognitive impairment to dementia among different antihypertensive medication groups.
ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HTN, hypertension; and RAS, renin-angiotensin system.

(Table 2). The results remained robust in the sensitivity analyses (Tables S3–S5).

Longitudinal Analysis of Cognitive Function Change

In general, compared to hypertension-no antihypertensives group, hypertension-ARB group had a lower increase of CDR-SB score from baseline (β=−0.20 [95% CI, −0.37 to −0.01]; P=0.042). Considering the interaction effects with time (years), hypertension-ARB group showed a slower annual increase of CDR-SB score from baseline (β=−0.43 [95% CI, −0.66 to −0.20]; P<0.001; P for interaction=0.002), a slower annual increase of ADAS-Cog-13 score from baseline (β=−1.14 [95% CI, −1.95 to −0.32]; P=0.006; P for interaction=0.045), a slower annual decline of Rey Auditory Verbal Learning Test score from baseline (β=1.33 [95% CI, 0.49–2.16]; P=0.002; P for interaction=0.020). Although the P for interaction was not significant, hypertension-ARB group showed a slower annual decline of MMSE score from baseline (β=0.40 [95% CI, 0.06–0.74]; P=0.022; P for interaction=0.091; Table 3, Figure 3).

Table 2. Hazard Ratios for Progression From Mild Cognitive Impairment to Dementia Associated With Different Antihypertensive Medication Groups (N=390)

Groups	Model 1*		Model 2†	
	HR (95% CI)	*P* value‡	HR (95% CI)	*P* value‡
HTN-ARB vs HTN-ACEI	0.55 (0.32–0.94)	0.033	0.45 (0.25–0.81)	0.023
HTN-ARB vs HTN-other antihypertensives	0.52 (0.30–0.90)	0.029	0.49 (0.27–0.89)	0.037
HTN-ARB vs HTN-no antihypertensives	0.25 (0.14–0.44)	<0.001	0.31 (0.16–0.58)	0.001
HTN-ACEI vs HTN-other antihypertensives	0.96 (0.65–1.41)	0.821	1.09 (0.71–1.69)	0.685
HTN-ACEI vs HTN-no antihypertensives	0.45 (0.30–0.70)	<0.001	0.68 (0.41–1.15)	0.179
HTN-other antihypertensives vs HTN-no antihypertensives	0.47 (0.31–0.73)	0.001	0.63 (0.37–1.06)	0.121

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HR, hazard ratio; and HTN, hypertension.
*Model 1 was unadjusted.
†Model 2 was adjusted for age, sex, race, education length, ever alcohol abuse, ever smoker, family history of dementia, hyperlipidemia, coronary heart disease, atrial fibrillation, transient ischemic attack or stroke, diabetes, chronic kidney disease, antiplatelet agents, Alzheimer's disease medication user, Apo E status, body mass index, systolic and diastolic blood pressure, $A\beta_{1-42}$, t-tau, p-tau_{181}, the Sum of Boxes of the Clinical Dementia Rating scale and the Mini-Mental State Examination scores at baseline.
‡*P* value were corrected using Benjamini & Hochberg method.

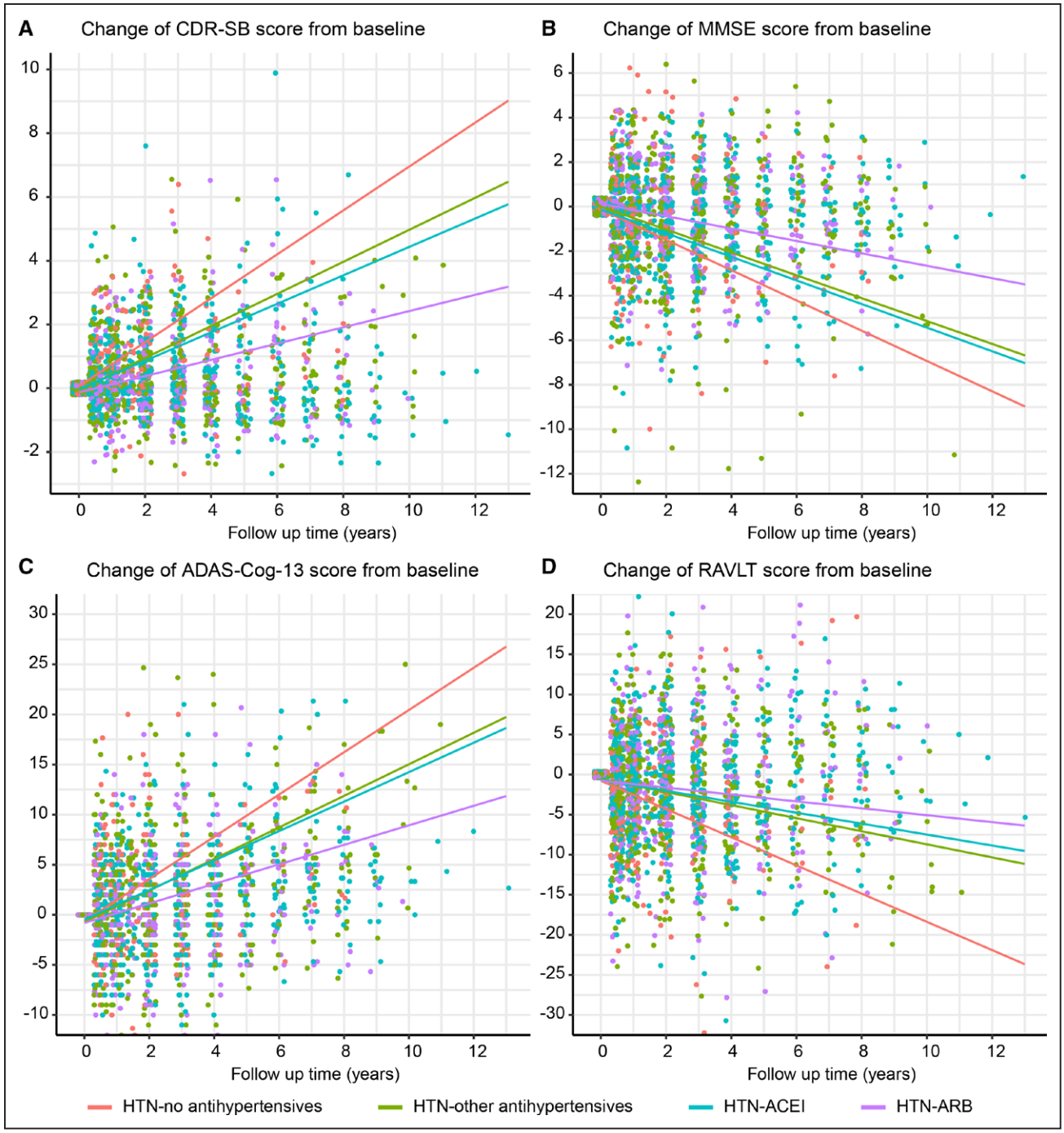

Figure 3. Change of the Sum of Boxes of the Clinical Dementia Rating scale (CDR-SB), Mini-Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive subscale test (ADAS-Cog-13), and Rey Auditory Verbal Learning Test (RAVLT) scores from baseline estimated by linear mixed-effects models using the method of marginal effects over the levels of factors among different antihypertensive medication groups.

ACEI indicates angiotensin-converting enzyme inhibitors; ADAS-Cog-13, the Alzheimer's Disease Assessment Scale-Cognitive subscale test; ARB, angiotensin receptor blocker; and HTN, hypertension.

DISCUSSION

In this retrospective cohort study in ADNI, to our knowledge, we first demonstrated that ARBs were associated with a lower risk of progression from MCI to dementia in patients with hypertension and MCI, compared with ACE inhibitor and other classes of AHMs. Longitudinal analysis of cognitive function change also showed that ARBs were associated with a slower annual increase of CDR-SB and ADAS-Cog-13 scores, and a slower annual decline of Rey Auditory Verbal Learning Test and MMSE scores from baseline, which further supported the neuroprotective effects of ARBs.

Comparison With Other Studies

Previous studies showed that BP lowering with AHMs was associated with a lower risk of incident dementia or cognitive impairment,[21] but the classes of AHMs associated with a reduced dementia risk were inconsistent.[22–26] In a rather large cohort study involving 819 491 predominantly male participants, Li et al[13] demonstrated that ARBs were associated with a lower incidence of dementia, compared with ACE inhibitors or other cardiovascular drugs. Two cohort studies conducted by Wharton et al[5,6] showed that in patients who had MCI and received AHMs, RAS-acting medication users were less likely to progress to AD and had fewer neurofibrillary tangles in brain than non-RAS users. However, it remains unclear whether and to what extent ARBs are superior to ACE inhibitors in reducing progression to dementia in patients with MCI. Through successive analyses for different AHMs groups, the current study demonstrated that in patients with hypertension and MCI, ARBs were associated with a lower risk of progression to dementia compared with ACE inhibitors and other classes of AHMs, which was consistent with several studies in that ARBs provided more neuroprotection than ACE inhibitors.[13,14,16–18,26] In an older study in the ADNI,[15] Hajjar et al found that ARBs were associated with a longitudinal decrease in CSF tau in patients with MCI. However, evidence based on biomarkers alone is insufficient, and there is a gap between these biomarkers and the clinical dementia outcome, especially when the underlying mechanisms are still not fully understood.[27] Instead, using the substantially updated data of the ADNI cohort that is still going on so far, with a larger sample size and a direct observation on the clinical dementia outcome, the current study addressed a key gap in the literature on the potential effect of ARBs in patients with MCI and further supported the superior neuroprotective effect of ARBs to ACE inhibitors.

A previous study showed that ARBs users had a small reduction in dementia risk compared with ACE inhibitors users only in the early follow-up period.[28] In the current study, however, the results remained robust in the 1-year lag analysis. It has been well established that CSF biomarkers for AD, including Aβ, t-tau, and p-tau, are associated with the risk of dementia or progression to dementia.[27,29] However, most previous studies did not take these biomarkers into account and might be confounded. In contrast, adjustment for these factors improved the quality of the current study.

The randomized trial by Hajjar et al[18] showed that in patients with MCI, 1-year treatment with candesartan had a superior executive function measured by the Trail Making Test Part B, compared with lisinopril. However, another recent trial in patients with clinically diagnosed AD failed to demonstrate a benefit of losartan versus placebo in reducing the rate of brain atrophy,[30] which was consistent with the failure of trials aiming to treat clinical dementia.[2] Therefore, the view is emerging that to achieve benefits, an intervention would likely need to be initiated at a preclinical stage (ie, MCI), rather than an advanced stage in the disease course.[31] Future clinical trials may be supposed to target patients with MCI to further investigate the effect of ARBs in reducing incident dementia.

Biological Plausibility

The mechanisms underlying the neuroprotective effects of ARBs may be explained by the angiotensin hypothesis.[8,9] In different terminal pathways of the RAS, activation of AT1Rs may promote neurotoxic mechanisms, such as oxidative stress, neuroinflammation, endothelial dysfunction, cerebral hypoperfusion, and cholinergic depletion,[32,33] while stimulation of AT2Rs could counteract these mechanisms.[10] Stimulation of AT4Rs helped learning and memory function in rodent models.[11] Additionally, ACE was shown to help Aβ degradation in experimental studies.[9] Overall, angiotensin II and IV may provide neuroprotection through AT2Rs and AT4Rs, although most evidence was based on experimental studies and the mechanisms were not fully understood.[10,11] ARBs, which selectively block the AT1Rs without inhibiting ACE and result in the relatively upregulated activities of AT2Rs and AT4Rs, and keep the pathway of Aβ degradation mediated by ACE intact, may offer superior protection than simultaneously lowering all the angiotensin receptors' activities with ACE inhibitors. Recent studies recognized that compared with angiotensin-inhibiting antihypertensives, angiotensin-stimulating antihypertensives conveyed a lower risk of incident cognitive impairment and dementia,[12,34] supporting the angiotensin hypothesis.

In addition, Hajjar et al. found that ARBs were associated with a longitudinal decrease in the CSF tau protein in MCI patients, which could also offer a possible biological mechanism for the effect of ARBs.[15] In a previous study, the prescription of ACE inhibitors was linked to a lower risk of cognitive deterioration, but this association lost statistical significance after adjusting for confounders.[35] Along with the studies from Hajjar et al,[15,18] our current study further supported the superior neuroprotective effect of ARBs to ACE inhibitors and showed a promising role of ARBs to prevent dementia in patients with MCI.

Strengths and Limitations

The ADNI is a multicenter prospective cohort with highly standardized, research-based definitions of MCI and AD. Extensive and frequent follow ups of cognitive state allow the timely detection of the progression from MCI

Table 3. Results of Linear Mixed-Effects Models: Cognitive Function Change From Baseline on CDR-SB, MMSE, ADAS-Cog-13, and RAVLT Scores Associated With Different Antihypertensive Medication Groups*

	CDR-SB		MMSE		ADAS-Cog-13		RAVLT	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
HTN-ARB	−0.20 (−0.37 to −0.01)	0.042	0.26 (−0.14 to 0.66)	0.224	−0.16 (−1.14 to 0.83)	0.754	0.02 (−1.37 to 1.41)	0.979
HTN-ACEI	−0.10 (−0.25 to 0.06)	0.258	−0.001 (−0.36 to 0.35)	0.992	0.18 (−0.69 to 1.06)	0.698	0.12 (−1.12 to 1.35)	0.857
HTN-other antihypertensives	−0.12 (−0.28 to 0.04)	0.161	0.13 (−0.23 to 0.50)	0.508	−0.08 (−0.97 to 0.82)	0.865	0.23 (−1.03 to 1.50)	0.728
HTN-no antihypertensives	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Time	0.69 (0.50 to 0.87)	<0.001	−0.68 (−0.96 to −0.40)	<0.001	2.11 (1.44 to 2.79)	<0.001	−1.76 (−2.46 to −1.05)	<0.001
HTN-ARB×time	−0.43 (−0.66 to −0.20)	<0.001	0.40 (0.06 to 0.74)	0.022	−1.14 (−1.95 to −0.32)	0.006	1.33 (0.49 to 2.16)	0.002
HTN-ACEI×time	−0.24 (−0.45 to −0.03)	0.024	0.15 (−0.16 to 0.46)	0.356	−0.64 (−1.39 to 0.12)	0.099	1.08 (0.28 to 1.86)	0.008
HTN-other antihypertensives×time	−0.19 (−0.39 to 0.03)	0.091	0.17 (−0.16 to 0.49)	0.315	−0.53 (−1.30 to 0.23)	0.176	0.94 (0.13 to 1.74)	0.022
HTN-no antihypertensives×time	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
P value for interaction	0.002		0.091		0.045		0.020	

ACEI indicates angiotensin-converting enzyme inhibitor; ADAS-Cog-13, the Alzheimer's Disease Assessment Scale-Cognitive subscale test; ARB, angiotensin receptor blocker; CDR-SB, the Sum of Boxes of the Clinical Dementia Rating scale; HTN, hypertension; MMSE, the Mini-Mental State Examination; and RAVLT, the Rey Auditory Verbal Learning Test.

*Models were adjusted for age, sex, race, education length, ever alcohol abuse, ever smoker, family history of dementia, hyperlipidemia, coronary heart disease, atrial fibrillation, transient ischemic attack or stroke, diabetes, chronic kidney disease, antiplatelet agents, Alzheimer's disease medication user, Apo E status, body mass index, systolic and diastolic blood pressure, $A\beta_{1\text{-}42}$, t-tau, p-tau_{181}, and the baseline score of corresponding cognitive test.

to dementia. The comprehensive assessments including cognition and CSF biomarkers improved the quality of our study. There were several limitations of our study. First, our study was an observational and retrospective analysis which might introduce biases (eg, medication information was self-reported, which could bring recall bias). Residual confounding is always possible in observational studies, especially in the case that the reason to choose a specific AHM could depend on comorbidities but also the judgment of the physicians. However, we conducted multiple sensitivity analyses to enhance the robustness of our findings. Second, there could be selection bias in our study since ADNI participants were recruited from the Alzheimer's Disease Cooperative Study centers and may not be very representative of the patients with cognitive impairment in the real world (eg, ADNI participants were mostly white and might be younger).[36] Third, due to the limitation of sample size, we failed to address the problem of multiple AHMs uses. Thus, we focused on ACE inhibitors and ARBs according to the angiotensin hypothesis. Ideally, researchers would exclude those with concomitant use of AHMs to separately investigate the impact of different classes of AHMs. Finally, information on AHMs dosage and duration was not considered in our analysis, as doses between different AHMs are difficult to compare, and group sizes would be too small if subgroups of doses and duration were made within 1 class of AHMs. Also, the blood-brain barrier permeability of drugs was not included, but some studies found that the blood-brain barrier-crossing RAS-acting medications may have more cognitive benefit.[5,19,37]

Perspectives

This retrospective cohort study showed that in patients with hypertension and MCI, ARBs were associated with a lower risk of progression to dementia compared with ACE inhibitors and other classes of AHMs. Our findings may have important implications for clinical practice for patients with MCI and hypertension but still warrant further investigations in larger prospective cohorts or clinical trials.

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Disclosures

None.

Supplemental Material

Tables S1–S5

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