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Associations between brain amyloid accumulation and the use of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers

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ABSTRACT

Some studies suggest that angiotensin II type 1 receptor blockers (ARBs) may protect against memory decline more than angiotensin-converting enzyme inhibitors (ACE-Is), but few have examined possible mechanisms. We assessed longitudinal differences between ARB versus ACE-I users in global and subregional amyloid-β accumulation by ^{18}F-florbetapir. In cognitively normal older adults (n= 142), propensity-weighted linear mixed-effects models showed that ARB versus ACE-I use was associated with slower amyloid-β accumulation in the cortex, and specifically in the caudal anterior cingulate and precuneus, and in the precentral and postcentral gyri. In amyloid-positive participants with Alzheimer's disease dementia or mild cognitive impairment (n = 169), ARB versus ACE-I use was not associated with different rates of amyloid-β accumulation. Apolipoprotein E ε4 carrier status explained some heterogeneity in the different rates of amyloid-β accumulation between users of ARBs versus ACE-Is in the study. Replicative studies and clinical trials are warranted to confirm potential benefits of ARBs on rates of amyloid-β accumulation in the contexts of Alzheimer's disease prevention and treatment.

1. Introduction

Midlife systolic hypertension is a risk factor for the incidence and progression of cognitive decline and Alzheimer's disease dementia (AD) (Kennelly et al., 2009; Perrotta et al., 2016; Skoog et al., 1996). Although the underlying mechanisms are incompletely understood, they are thought to involve reduced cerebral perfusion, oxidative stress, blood-brain barrier dysfunction, and increased deposition of amyloid-β (Aβ) (Carnevale et al., 2012; Tublin et al., 2019). Some (Ding et al., 2020; Duron et al., 2009; Li et al., 2010; Livingston et al., 2017; Yasar et al., 2013) but not all (Gelber et al., 2013; Peters et al., 2020; Walker et al., 2019; Xu et al., 2017) studies have broadly associated the use of antihypertensive agents with a reduced risk of cognitive decline or incident dementia. Due to differences in their antihypertensive mechanisms of action, and in their effects on pathways unrelated to blood pressure control, it has been hypothesized that different classes of

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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antihypertensives may vary in their effects on neurodegeneration and cognitive decline (Edwards et al., 2017; Lawlor et al., 2018).

Two of the most frequently prescribed antihypertensive drug classes are the angiotensin II receptor blockers (ARBs) and the angiotensin-converting enzyme inhibitors (ACE-Is), both of which act upon the renin-angiotensin system (RAS) (Rodgers and Patterson, 2001). Despite similarities in their biological targets, indications, and adverse effect profiles (Li et al., 2014), evidence has emerged suggesting a potential divergence in their benefit to those with or at risk for AD dementia. Studies have compared ACE-Is and ARBs with respect to indices of neurodegeneration, finding that ARB use was associated with less atrophy (Edwards et al., 2017; Moran et al., 2019), but the molecular basis for this observation is unclear. Several studies have also identified decreased dementia incidence among ARB users relative to ACE-I users (Barthold et al., 2018; Bohlken et al., 2019; Goh et al., 2015), though others have not (Ding et al., 2020).

It has been suggested that ACE-Is and ARBs may have differential effects on Aβ processing (Ashby et al., 2016; Edwards et al., 2017; Fournier et al., 2009; Kehoe, 2018). ACE-Is act upstream in the RAS pathway, inhibiting the angiotensin-converting enzyme 1 (ACE-1) directly, potentially leading to a decrease in Aβ degradation catalyzed by the N-terminus of the ACE-1 enzyme (Hemming and Selkoe, 2005; Zou et al., 2007). In contrast, ARBs act downstream, preventing the binding of angiotensin II to the angiotensin II type 1 receptor (AT1R), thereby blunting the RAS-mediated systems that contribute to increased blood pressure without impacting ACE-1-mediated Aβ metabolism (Danielyan et al., 2010; Drews et al., 2019; Oba et al., 2005). By maintaining elevated angiotensin II levels, ARBs may also facilitate the activation of the AT2R, Mas receptor, and other receptors in the regulatory RAS pathways which mediate anti-inflammatory, vasodilatory, and neuroprotective effects, both directly, and indirectly through the upregulation of ACE-2-mediated conversion of angiotensin II into angiotensin (1–7) (Evans et al., 2020; Furuhashi et al., 2015; Paz Ocaranza et al., 2020; Vaduganathan et al., 2020). Preclinical evidence suggests that ARBs upregulate the expression of enzymes directly involved in the catabolism and clearance of Aβ peptides, including neprilysin, transthyretin, and insulin-degrading enzyme (Benson et al., 2004; Drews et al., 2019; Grimm et al., 2013; Wang et al., 2007). A number of animal studies have demonstrated positive effects of ARBs in reducing the accumulation of Aβ, and in the prevention of Aβ-related vascular dysregulation (Mogi et al., 2008; Shuko et al., 2009; Wang et al., 2007).

In support of the hypothesis that ACE-Is versus ARBs may have different effects on amyloid in humans, one cross-sectional post-mortem human study found that ARB use was associated with reduced amyloid pathology compared to other antihypertensive drugs (Hajjar et al., 2012). A separate cross-sectional study found that ARB use compared to the use of other antihypertensive classes was associated with lower PiB-PET Aβ deposition in cognitively normal participants (Glodzik et al., 2016). Another study compared ARB users to users of other antihypertensives longitudinally, finding attenuated age-related reductions in $A\beta_{1\text{-}42}$ and lower phosphorylated tau concentrations in the cerebrospinal fluid, and lower rates of incident dementia (Nation et al., 2016). The latter two did not compare ARBs to ACE-Is specifically, so a possible differential effect of ARBs versus ACE-Is on Aβ accumulation in brain tissue over time has yet to be examined in living people.

This study aimed to determine associations between ARB versus ACE-I use and Aβ accumulation in the brain, both globally and subregionally, in older adults with normal cognition, mild cognitive impairment (MCI), or mild dementia due to AD from the Alzheimer's Disease Neuroimaging Initiative (ADNI). It was hypothesized that ARB use would be associated with a slower rate of Aβ accumulation relative to ACE-I use. Previously, associations between ARB versus ACE-I use with cognition have been mixed, even among studies that showed differential relationships with atrophy (Edwards et al., 2017; Ho and Nation, 2017; Moran et al., 2019) for reasons that are not clear. Therefore, this study further sought to identify potential sources of heterogeneity in Aβ accumulation that may explain discrepancies in the previous findings. Specifically, due to the role of the apolipoprotein E (*APOE*) ε4 allele as a risk factor for AD, a possible moderating effect of *APOE* carrier status was examined with respect to the relationships between these drugs and amyloid accumulation. Ultimately, the goal of this work is to advance insight into possible differential benefits of ARBs and ACE-Is on Aβ accumulation in patients who are at risk for AD.

2. Methods

2.1. Data source

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Enrolled participants range from 55 to 90 years of age. Inclusion criteria specify permitted medications stable for 4 weeks before screening, a study partner who can accompany participants to visits, a Geriatric Depression Scale score lower than 6, a Hachinski Ischemic Scale score less than or equal to 4, adequate visual and auditory acuity for the purposes of neuropsychological testing, a minimum of 6 grades of education or equivalent work history, and the ability to speak English or Spanish fluently. Exclusion criteria for participants with normal cognition and MCI include any significant neurological disease or history of significant head trauma. The dataset was downloaded on or before December 8, 2019 and reflects the status of the database at that point. ADNI was conducted according to Good Clinical Practice guidelines, the Declaration of Helsinki, US 21CFR Part 50-Protection of Human Subjects, and Part 56-Institutional Review Boards, following all relevant state and federal Health Insurance Portability and Accountability Act (HIPAA) regulations. For up-to-date information, see www.adni-info.org.

2.2. Participant selection

Participants with clinically normal cognition (CN), MCI, or AD, who were using either an ACE-I or an ARB and who had PET Aβ data available for ≥1 observation were selected from ADNI-1, ADNI-Grand Opportunity (ADNI-GO), and ADNI-2 for analysis. A further inclusion criterion for the AD/MCI group was amyloid positivity (i.e., standardized uptake value ratio [SUVR] on an ^{18}F-AV-45 [^{18}F-florbetapir] PET scan above 0.79). Participants in the cognitively normal group were not excluded on the basis of amyloid burden. Those using both medication classes were excluded. Participants were classified as MCI on the basis of (1) subjective memory concerns expressed by the study participant, their study partner, or a clinician; (2) a rating of 0.5 on the Clinical Dementia Rating; (3) a score of 24 or greater on the Mini-Mental State Examination; (4) an absence of depression, as defined by a score less than 5 on the Geriatric Depression Scale; (5) a score below the education-adjusted cutoffs on the Wechsler Memory Scale-Revised Logical Memory II subtest, Story A; and (6) preservation of general cognitive and functional ability to an extent that would preclude a diagnosis of AD. Participants were classified as AD in accordance with National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD. A subset of these

individuals with a diagnosed history of hypertension, as indicated by their medical records, was identified for subgroup analyses.

2.3. Drug exposures

Medication exposure status was retrospectively ascertained through manual review of prescription history available in the ADNI database. For observations where medication records were unavailable or incomplete, data from the preceding time point with available information were extrapolated. Exposure to other antihypertensive medications used concomitantly by these participants, including β-blockers, calcium channel blockers, and diuretics was also ascertained to control for the effects of these drug classes in the analyses.

2.4. PET β-amyloid outcomes

The primary outcome was ^{18}F-florbetapir SUVR in a cortical summary region of interest comprised of the frontal lobe, anterior/posterior cingulate, lateral parietal lobe, and lateral temporal lobe, which was normalized to a composite reference region comprised of the whole cerebellum, brainstem, pons, and eroded subcortical white matter, as recommended for longitudinal analyses (Landau et al., 2015). The methodology of ^{18}F-florbetapir synthesis and image acquisition details are described in detail elsewhere (Landau et al., 2013). Briefly, ^{18}F-florbetapir images consisted of 4×5 minute frames acquired 50–70 minutes post-injection which were realigned, averaged, resliced to a common voxel size of 1.5 mm^3, and smoothed to a common resolution of 8 mm in full width at half-maximum. T1-weighted magnetic resonance imaging images were acquired concurrently and used as a structural template to establish cortical regions of interest and reference regions in native space for each subject using FreeSurfer. Baseline florbetapir scans for individual participants were co-registered to T1-weighted structural images accordingly, and weighted cortical retention indices were extracted to create a mean cortical SUV, which was then divided by the composite reference region as described previously to determine a normalized cortical SUVR (Landau et al., 2015). In addition to summary cortical SUVR, Aβ deposition was analyzed in subregions associated with early-stage AD (inferior temporal lobe, precuneus, cuneus, caudal anterior cingulate, fusiform) and subregions associated with intermediate or late-stage AD (medial temporal lobe, lateral occipital lobe, precentral gyrus, postcentral gyrus) (Grothe et al., 2017; Mattsson et al., 2019) with the intention of probing potential region-specific effects of ARBs and ACE-Is on the progression of amyloid spread across cognitively normal and Aβ+ AD/MCI groups.

2.5. Statistical analyses

The cognitively normal and AD/MCI groups were analyzed separately. Analyses were conducted using R 3.6.2, and figures were created using the ggplot2 package (Gómez-Rubio, 2017). Descriptive statistics were generated to characterize the study cohort according to all study variables. One-way analysis of variance was used to compare the groups for continuous variables, while χ^2 or Fisher's exact testing was used to compare the groups for nominal or categorical variables at baseline.

In order to quantify the associations between use of an ARB and an ACE-I with longitudinal changes in Aβ burden, random-intercepts linear mixed-effects regression models were used (lme4 package) (Bates et al., 2015). Standardized coefficients (β) were used to express the magnitude of the effect size of the associations, with medication use × time as the term of interest. Models were adjusted for clinically relevant covariates interacted with time, including age, sex, years of education, baseline Mini-Mental State Examination score, *APOE* ε4 status (allele present vs. not present), systolic blood pressure, and concurrent use of antihypertensive medications other than ARBs or ACE-Is. In models including all participants, diagnosis (cognitively normal vs. AD/MCI) was also controlled for.

Models were further adjusted for potential confounding by indication through the utilization of inverse probability of treatment weighting (ipw package) (van der Wal and Geskus, 2011). Marginal structural models were used to determine treatment probability weights based on time-varying confounders known to influence the likelihood to be prescribed an ARB or an ACE-I. The following factors were selected from the 2004 NIH National High Blood Pressure Education Program guidelines: race (African American vs. not), which was included as a stabilizing factor; diabetes, a history of myocardial infarction, a history of transient ischemic attack, or a history of stroke (Chobanian et al., 2003). Vascular risk factors and comorbidities were ascertained through manual review of medical history and physical examination data available through the ADNI database.

The *APOE* ε4 gene polymorphism has emerged as a strong risk factor for late-onset AD and accelerated disease progression, and it is associated with early seeding of Aβ pathology, enhanced Aβ aggregation, and perturbation of Aβ clearance (Liu et al., 2017; Verghese et al., 2013). Therefore, to explore potential heterogeneity, we investigated *APOE* ε4 allele carrier status as a potential modifier of the associations between ARB or ACE-I use and Aβ deposition over time, using a drug × *APOE* ε4 × time interaction term. We then determined the conditional associations between drug class and Aβ deposition over time in *APOE* ε4 carriers and non-carriers to evaluate the effect size in each subgroup.

Additional sensitivity analyses were conducted. Because most, but not all users of ARBs or ACE-Is had hypertension, we repeated the main models in a subgroup of people who had a diagnosed history of hypertension. Post hoc models were also considered that included additional covariates—specifically baseline white matter hyperintensity (WMH) volumes, time-varying body mass index (BMI), and statin use, to ensure that the main findings were robust to these measures. Furthermore, a post hoc model in which observations from users of ARBs or ACE-Is were censored upon switching between the 2 drug classes were conducted in order to ascertain potential cross-over effects, although the marginal structural models used for propensity weighting account for previous time-dependent exposure. Finally, as prescription practices may differ geographically, from site to site, ADNI site identifiers were incorporated into the propensity weighting in a post hoc model.

3. Results

3.1. Subject characteristics

Baseline demographics and clinical characteristics are shown in Table 1. From a total of 1740 participants in ADNI-1, ADNI-GO, and ADNI-2, the study cohort included 311 participants (142 CN and 169 Aβ+ AD/MCI) who had medication records indicating use of an ACE-I or an ARB, available PET Aβ observations, and other data required for covariate adjustment (Fig. 1). The mean number of observations was 2.20 for participants who were CN at baseline and 1.69 for Aβ+ AD/MCI participants at baseline. Among those with at least 1 follow-up visit, the mean duration of follow-up did not differ among CN (ARB: 3.6 ± 1.7 years; ACE-I: 4.1 ± 1.8 years; $p = 0.187$) or Aβ+ AD/MCI participants (ARB: 3.2 ± 1.8 years; ACE-I: 3.5 ± 1.8 years; $p = 0.501$). There were 109 ARB users and 204 ACE-I users at baseline. Similar proportions of ARB and ACE-I users were using 2 or more antihypertensive medications at baseline (51.4% and 52.9%, respectively).

3.2. ARBs versus ACE-Is and amyloid accumulation in cognitively normal participants

Among cognitively normal participants, ARB use was associated with a lower rate of global Aβ accumulation over time, compared to ACE-I users (β [95% Confidence Interval] = −0.049 [−0.085, −0.013], $p = 0.008$; Table 2, Fig. 2A). This association was consistent in the subset of participants with a confirmed history of hypertension (β = −0.053 [−0.091, −0.015], $p = 0.008$, $n = 133$).

On a sub-regional level, ARBs were associated with reduced Aβ accumulation over time relative to ACE-Is in areas associated with early Aβ pathology, including the precuneus and the caudal anterior cingulate (Table 2). Among regions associated with later stages of AD progression, there were no differences between ARBs and ACE-Is in the lateral occipital lobe, nor the medial temporal lobe; however, a significant difference was observed in both the precentral and postcentral gyri (Table 2).

3.3. ARBs versus ACE-Is and amyloid accumulation in Aβ+ AD/MCI participants

Among Aβ+ participants with AD or MCI, there was no significant difference in the rate of global Aβ accumulation over time in ARB compared to ACE-I users (β = 0.020 [−0.037, 0.077], $p = 0.495$; Table 2, Fig. 2B). Similarly, there was no effect detected in the subset of participants with a confirmed history of hypertension (β = 0.007 [−0.054, 0.069], $p = 0.808$, $n = 153$). Moreover, there were no significant group differences in Aβ accumulation in early or late subregions examined (Table 2).

3.4. ARBs versus ACE-Is in all APOE ε4 carriers and APOE ε4 non-carriers

Among all participants, a significant interaction between drug exposure and *APOE* ε4 status over time was observed (drug exposure × *APOE* status × time interaction $p = 0.046$), indicating that ARB use was associated with a significantly slower rate of Aβ accumulation in *APOE* ε4 non-carriers compared to *APOE* ε4 carriers. These interactions were notable in the caudal anterior cingulate and the precuneus (conditional associations between *APOE* ε4 carrier status and antihypertensive drug class are shown in Supplementary Table A1).

3.5. ARBs versus ACE-Is in cognitively normal APOE ε4 carriers and APOE ε4 non-carriers

In cognitively normal people, ARB use was associated with slower global Aβ accumulation in *APOE* ε4 non-carriers (β = −0.046 [−0.085, −0.008], $p = 0.018$; Table 3, Fig. 3A). Among this group, significant differences between ACE-I and ARB users were also noted regionally in the precuneus, cuneus, caudal anterior cingulate fusiform, and precentral gyrus (Table 3). In contrast, there was no difference in Aβ accumulation between ARB versus ACE-I use among *APOE* ε4 carriers globally (β = −0.017 [−0.096, 0.063], $p = 0.677$; Fig. 3B); however, a significant difference was seen in the lateral occipital lobe.

3.6. ARBs versus ACE-Is in Aβ+ AD/MCI APOE ε4 carriers and APOE ε4 non-carriers

Among Aβ+ people with AD/MCI, there were no differences between people using ARBs versus ACE-Is in their rates of whole-brain Aβ accumulation, either in *APOE* ε4 non-carriers (β = 0.010 [−0.067, 0.086], $p = 0.813$) or in *APOE* ε4 carriers (β = 0.040 [−0.033, 0.113], $p = 0.284$); furthermore, no association was seen in any subregion analyzed (Supplementary Table A2); however, there was a drug exposure × *APOE* status × time interaction observed in the caudal anterior cingulate, where ARBs were associated with a lower rate of Aβ accumulation in ε4 non-carriers, but not ε4 carriers ($p = 0.015$).

Table 1
Baseline demographics and characteristics by diagnosis and medication class

	Cognitively normal			AD/MCI Aβ+		
	ARB ($n = 50$)	ACE-I ($n = 92$)	p value	ARB ($n = 59$)	ACE-I ($n = 110$)	p value
Baseline demographics						
Age (y)	75.0 (6.9)	75.8 (6.7)	0.508	74.4 (6.7)	76.4 (7.3)	0.086
Female	**31 (62.0%)**	**36 (39.1%)**	**0.009**	28 (47.5%)	41 (37.3%)	0.199
Race (Caucasian)	46 (92.0%)	81 (88.0%)	0.464	53 (89.8%)	96 (87.3%)	0.080
BMI (kg/m^2)	28.2 (6.1)	27.3 (4.9)	0.347	28.4 (5.7)	27.2 (4.2)	0.099
Education (y)	16.2 (3.0)	16.7 (2.4)	0.237	15.5 (2.9)	15.8 (2.8)	0.588
Systolic BP (mm Hg)	139.8 (18.6)	135.1 (16.2)	0.120	134.2 (19.4)	135.4 (17.9)	0.679
Dementia-related measures						
Baseline MMSE	28.9 (1.2)	28.8 (1.4)	0.748	25.5 (5.0)	26.2 (2.9)	0.273
APOE ε4 carrier	13 (26.0%)	32 (34.8%)	0.283	33 (56.9%)	69 (62.7%)	0.462
Baseline WMH (cc)[a]	2.4 (3.9)	4.5 (6.6)	0.052	6.7 (8.2)	5.8 (9.1)	0.926
Comorbidities at baseline						
Hyperlipidemia	32 (64.0%)	52 (56.5%)	0.387	45 (76.3%)	72 (65.5%)	0.240
Hypertension	49 (98.0%)	84 (91.3%)	0.118	56 (94.9%)	98 (89.1%)	0.204
Stroke/TIA history	6 (12.0%)	7 (7.6%)	0.386	3 (5.1%)	8 (7.3%)	0.583
Myocardial infarct	4 (8.0%)	2 (2.2%)	0.099	3 (5.1%)	5 (4.5%)	0.875
Diabetes	**13 (26.0%)**	**13 (14.1%)**	**0.043**	15 (25.4)	27 (24.5%)	0.900
Coronary artery disease	3 (6.0%)	11 (12.0%)	0.255	4 (6.8%)	9 (8.2%)	0.744
Concomitant medications						
β-Blockers	11 (22.0%)	14 (15.2%)	0.311	11 (18.6%)	25 (22.7%)	0.537
CCBs	13 (26.0%)	12 (13.0%)	0.053	10 (16.9%)	22 (20.0%)	0.629
DRTCs	16 (32.0%)	33 (35.9%)	0.643	16 (27.1%)	33 (30.0%)	0.694
Statins	33 (66.0%)	56 (60.9%)	0.546	47 (79.7%)	80 (72.7%)	0.320

Continuous variables and categorical variables were reported in observed/unweighted mean (SD) and proportion, respectively. Bold indicates $p < 0.05$.
Key: Aβ, amyloid-β; ACE-I, angiotensin-converting enzyme inhibitor; AD, Alzheimer's disease; *APOE*, apolipoprotein E; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; df, degrees of freedom; DRTC, diuretics; IQR, interquartile range; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SD, standard deviation; TIA, transient ischemic attack; WMH, white matter hyperintensity.
[a] WMH values presented as median (IQR) due to non-normality.

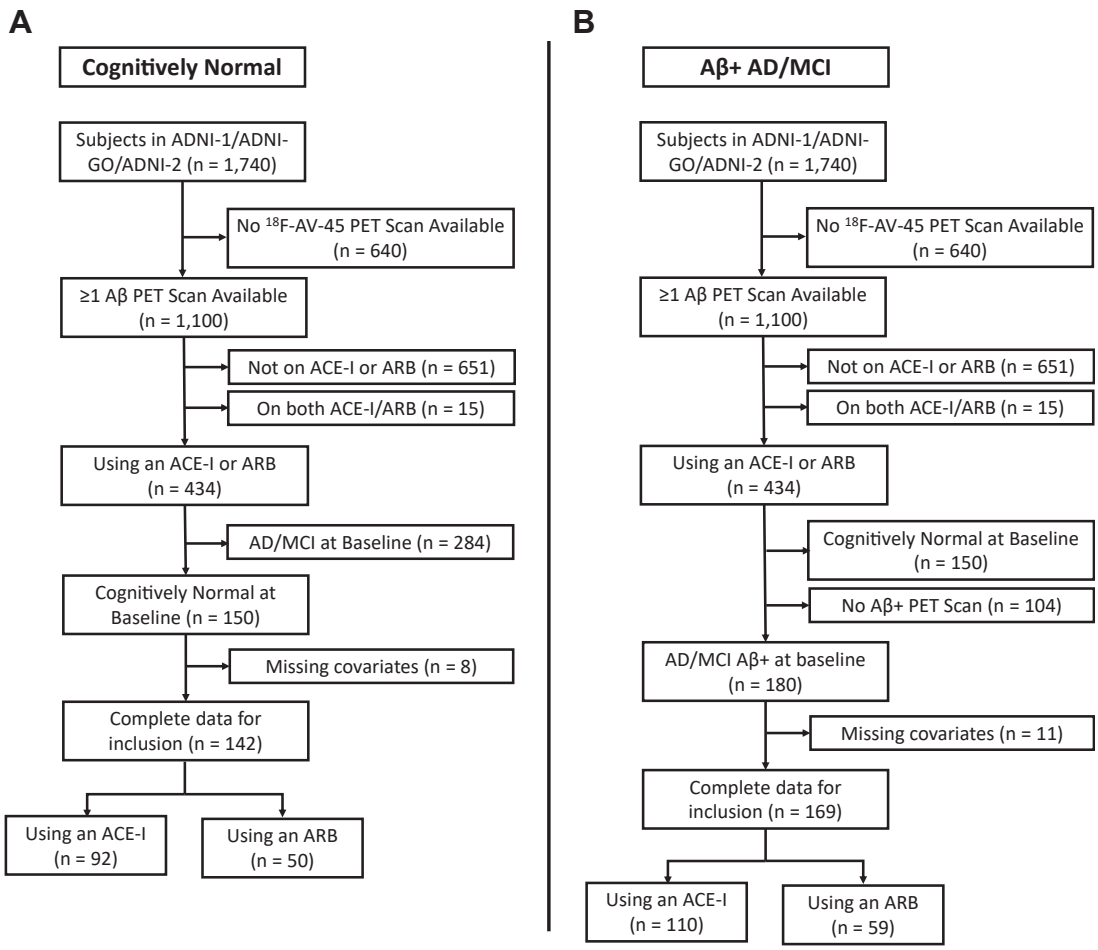

Fig. 1. Process for the selection of participants for inclusion in CN and AD/MCI Aβ+ analysis groups: (A) cognitively normal participant selection and (B) Aβ+ AD/MCI participant selection. Participants included in the final AD/MCI group required an Aβ+ pet scan (indicating elevated amyloid above the positive cutoff of 0.79). Abbreviations: Aβ, amyloid-β; AD, Alzheimer's disease; CN, normal cognition; MCI, mild cognitive impairment.

3.7. Post hoc models

Including baseline WMH volume, time-varying BMI, or statin use as an additional covariate did not alter the associations in global amyloid. In cognitively normal people, ARB use remained associated with a slower rate of global brain amyloid accumulation compared to ACE-I use in models adjusted for baseline WMH volume (β = −0.066 [−0.111, −0.018], p = 0.007), time-varying BMI (β = −0.045 [−0.083, −0.006], p = 0.024), or statin use (β = −0.047 [−0.083, −0.011], p = 0.013). As in the models with covariates chosen a priori, no significant associations between ACE-I versus ARB use and global amyloid accumulation emerged in the Aβ+ AD/MCI subgroup upon consideration of these factors. Furthermore, in models where subject data were censored after switching between an ACE-I and an ARB, associations remained consistent both in cognitively normal (β = −0.053 [−0.087, −0.018], p = 0.003) and in Aβ+ AD/MCI (β =

Table 2
Associations between ARB versus ACE-I use and Aβ accumulation in cognitively normal and Aβ+ AD/MCI participants

Brain region	Cognitively normal				AD/MCI Aβ+			
	Beta [95% CI]	| t |	df	p-value	Beta [95% CI]	| t |	df	p-value
Global amyloid	**−0.049 [−0.085, −0.013]**	**2.67**	**160.03**	**0.008**	0.020 [−0.037, 0.077]	0.68	116.06	0.495
Early regions								
Inferior temporal lobe	−0.030 [−0.073, 0.014]	1.33	160.10	0.184	−0.004 [−0.065, 0.058]	0.12	119.26	0.905
Precuneus	**−0.049 [−0.088, −0.011]**	**2.49**	**161.01**	**0.014**	0.019 [−0.037, 0.075]	0.67	116.68	0.507
Cuneus	−0.032 [−0.085, 0.020]	1.22	162.94	0.225	0.025 [−0.033, 0.083]	0.85	118.87	0.395
Caudal anterior cingulate	**−0.054 [−0.101, 0.006]**	**2.22**	**165.54**	**0.028**	−0.006 [−0.086, 0.073]	0.16	124.12	0.871
Fusiform	−0.032 [−0.079, 0.015]	1.31	169.91	0.191	−0.001 [−0.065, 0.062]	0.04	119.41	0.965
Mid-late regions								
Lateral occipital lobe	−0.022 [−0.076, 0.032]	0.79	159.51	0.429	0.001 [−0.065, 0.066]	0.02	118.78	0.987
Medial temporal lobe	−0.020 [−0.064, 0.026]	0.85	163.38	0.397	0.025 [−0.041, 0.091]	0.74	120.60	0.463
Precentral gyrus	**−0.081 [−0.129, −0.034]**	**3.37**	**159.22**	**0.001**	0.022 [−0.048, 0.093]	0.63	119.85	0.533
Postcentral gyrus	**−0.056 [−0.104, −0.008]**	**2.31**	**158.51**	**0.022**	0.033 [−0.035, 0.102]	0.96	119.25	0.341

Bold indicates p< 0.05.
Key: Aβ, amyloid-β; ACE-I, angiotensin-converting enzyme inhibitor; AD, Alzheimer's disease; ARB, angiotensin II receptor blocker; CI, confidence interval; df, degrees of freedom; MCI, mild cognitive impairment.

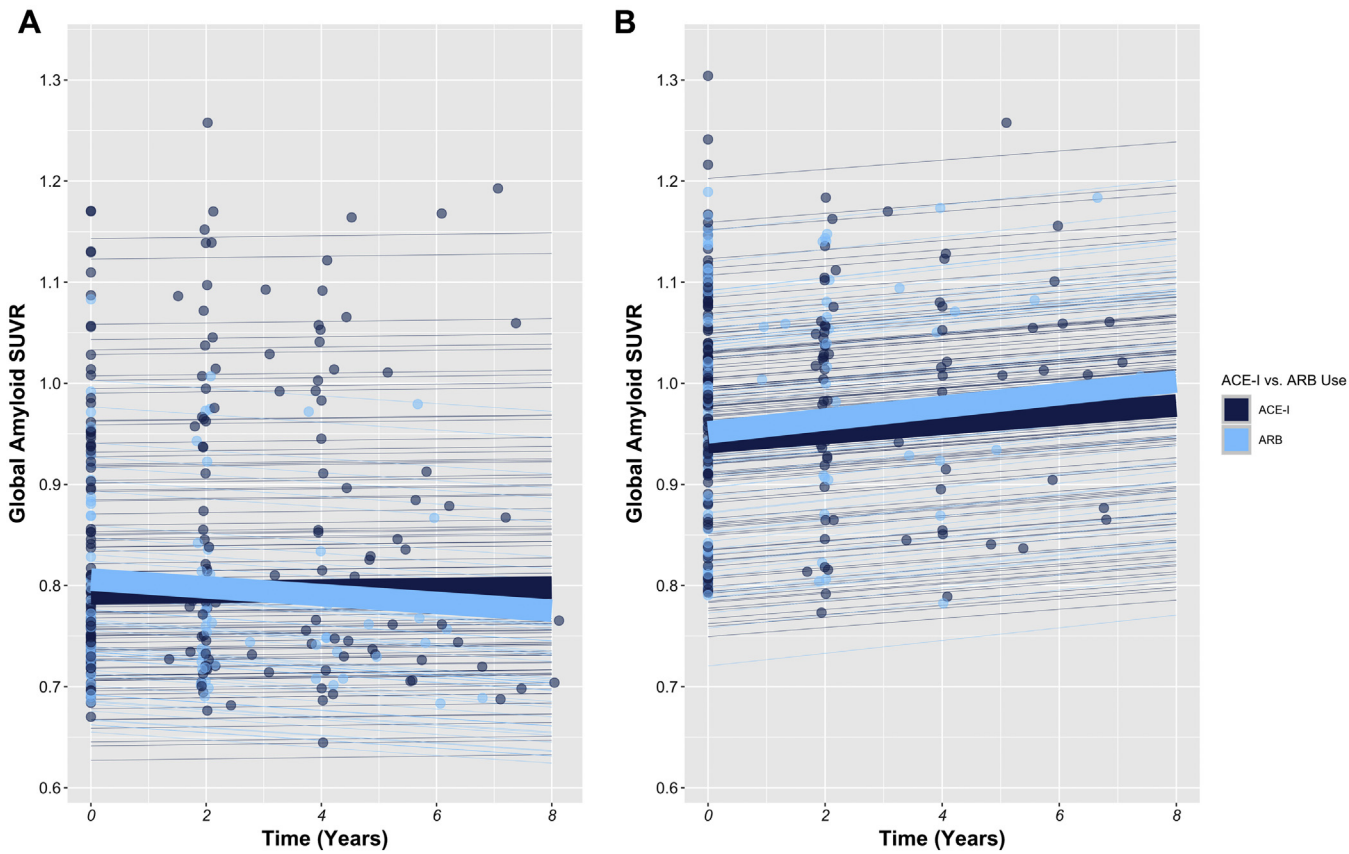

Fig. 2. Associations between ARB versus ACE-I use and global Aβ accumulation in (A) cognitively normal and (B) Aβ+ AD/MCI participants. Thick lines represent the overall predicted treatment effects, adjusted for covariates; thin lines represent predicted associations for individual participants. Abbreviations: Aβ, amyloid-β; ACE-I, angiotensin-converting enzyme inhibitor; AD, Alzheimer's disease; ARB, angiotensin II receptor blocker; MCI, mild cognitive impairment.

0.021 [−0.032, 0.074], $p = 0.438$). Moreover, in a model including ADNI site identifiers in the propensity weighting model, associations with global amyloid did not change in either subgroup.

4. Discussion

4.1. Findings in clinically normal adults

This study compared longitudinal associations between ARB versus ACE-I use with Aβ deposition in groups of asymptomatic and symptomatic older adults at different stages of cognitive impairment due to AD. In cognitively normal people, use of an ARB was associated with a slower rate of Aβ accumulation over time as compared to use of an ACE-I. These findings are broadly consistent with lower amyloid pathology (Hajjar et al., 2012), with a lower likelihood of neuropathological (Hajjar et al., 2012) or clinical (Nation et al., 2016) AD diagnosis, with lower PiB-PET Aβ cross-sectionally (Glodzik et al., 2016), and with slower progression of CSF $A\beta_{1\text{-}42}$ and phosphorylated tau biomarkers over time (Nation et al., 2016) previously associated with ARB use. Here we show that the relationship with Aβ deposition among clinically normal people is specific to ARBs, even compared to the ACE-I anti-

Table 3
Conditional associations between ARB versus ACE-I use and Aβ accumulation in cognitively normal *APOE* ε4 carriers and non-carriers

Brain region	Cognitively normal *APOE* ε4 non-carriers				Cognitively normal *APOE* ε4 carriers			
	Beta [95% CI]	| *t* |	df	*p*-value	Beta [95% CI]	| *t* |	df	*p*-value
Global amyloid	**−0.046 [−0.085, −0.008]**	**2.39**	**164.58**	**0.018**	−0.017 [−0.096, 0.063]	0.42	164.61	0.677
Early regions								
Inferior temporal lobe	−0.035 [−0.081, 0.011]	1.50	166.46	0.135	−0.001 [−0.096, 0.094]	0.02	166.80	0.987
Precuneus	**−0.054 [−0.094, −0.013]**	**2.60**	**164.70**	**0.010**	−0.010 [−0.094, 0.075]	0.23	164.78	0.822
Cuneus	−0.015 [−0.070, 0.040]	0.53	169.76	0.597	−0.062 [−0.176, 0.053]	1.05	170.45	0.294
Caudal anterior cingulate	**−0.075 [−0.124, −0.026]**	**3.01**	**167.91**	**0.003**	0.030 [−0.072, 0.133]	0.58	168.41	0.565
Fusiform	−0.035 [−0.085, 0.014]	1.41	167.92	0.159	−0.008 [−0.110, 0.095]	0.15	168.39	0.883
Mid-late regions								
Lateral occipital lobe	0.004 [−0.052, 0.060]	0.15	168.92	0.883	**−0.125 [−0.242, 0.008]**	**2.10**	**169.70**	**0.037**
Medial temporal lobe	−0.010 [−0.057, 0.037]	0.41	167.77	0.682	−0.062 [−0.160, 0.035]	1.25	168.19	0.213
Precentral gyrus	**−0.067 [−0.118, −0.016]**	**2.60**	**167.95**	**0.010**	−0.063 [−0.169, 0.043]	1.17	168.47	0.245
Postcentral gyrus	−0.038 [−0.089, 0.012]	1.48	168.24	0.140	−0.065 [−0.171, 0.041]	1.21	168.83	0.229

Bold indicates $p < 0.05$.
Key: Aβ, amyloid-β; ACE-I, angiotensin-converting enzyme inhibitor; *APOE*, apolipoprotein E; ARB, angiotensin II receptor blocker; CI, confidence interval; df, degrees of freedom.

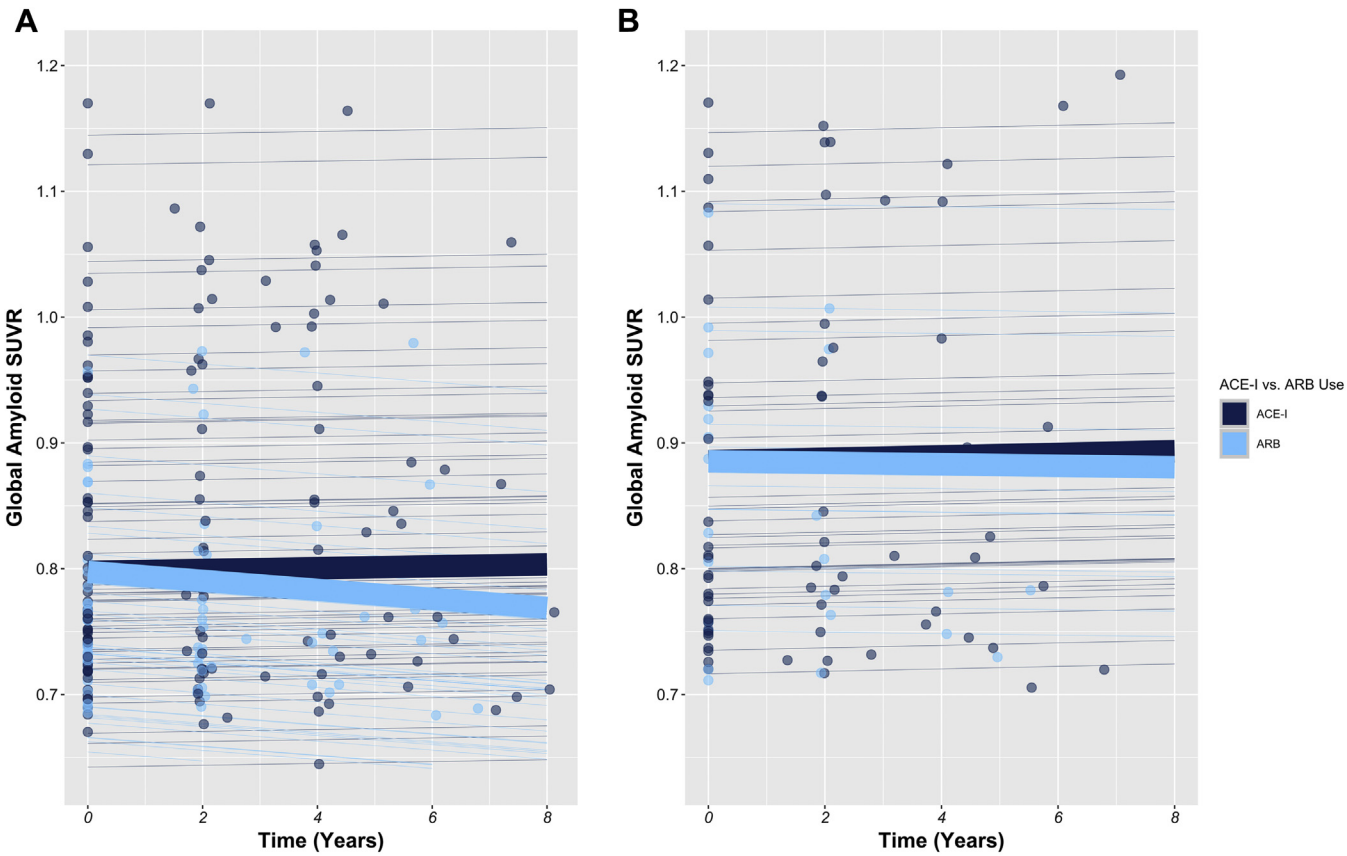

Fig. 3. Associations between ARB or ACE-I use and global Aβ accumulation over time in (A) cognitively normal *APOE* ε4 non-carriers and (B) cognitively normal *APOE* ε4 carriers. Thick lines represent the overall predicted treatment effects, adjusted for covariates; thin lines represent predicted associations for individual participants. Abbreviations: Aβ, amyloid-β; ACE-I, angiotensin-converting enzyme inhibitor; *APOE*, apolipoprotein E; ARB, angiotensin II receptor blocker.

hypertensives that also target specifically the RAS system. Therefore, to our knowledge, this study provides the first longitudinal clinical evidence that speaks directly to the hypothesized anti-amyloid effect of ARBs. The question is clinically relevant because ACE-Is and ARBs have similar indications and clinical uses, and often they could be prescribed interchangeably. The findings may be clinically important because Aβ accumulation can predict cognitive decline in clinically normal adults (Rabin et al., 2019a).

In further analyses, we examined whether there might be differential effects of ARBs and ACE-Is in sub-regions associated typically with early versus mid/late-stage Aβ accumulation as selected a priori based on amyloid PET staging studies (Grothe et al., 2017; Mattsson et al., 2019). Associations between the use of ACE-Is versus ARBs and amyloid accumulation were identified in the precuneus and in the caudal anterior cingulate, both of which were identified by Palmqvist et al. (2017) to be involved in the earliest stages of Aβ accumulation among non-demented people. Both of these sub-regions fall within the default mode network, a functional network of brain regions which show synchronous activation at rest, and increased activity in a task-free state (Mevel et al., 2011; Palmqvist et al., 2017). A distinct pattern of activity in the default mode network distinguishes incipient AD from normal aging (Greicius et al., 2004). This suggests that ARBs may offer benefits on amyloid accumulation in brain regions associated with the initial pathogenesis of AD. Effects were also observed in both the precentral and postcentral gyri, regions associated with mid-stage or late-stage AD. Overall, these subregional findings do not distinguish effects of ACE-Is versus ARBs between early versus later stages of amyloid accumulation, but the findings in the precuneus and caudal anterior cingulate specifically in asymptomatic people would be consistent with benefits of ARB use in the context of early AD pathogenesis for the purposes of AD prevention.

4.2. *Findings in Aβ+ AD/MCI patients*

In contrast to the findings in cognitively normal people, no significant differences were observed between ACE-I and ARB users among Aβ+ participants with AD or MCI. The reason for this is unclear; however, a plateau in the natural course of Aβ accumulation has been described in AD (Jack et al., 2013; Villemagne et al., 2013) and the dynamics of the amyloid cascade appear to be different between clinically normal and AD groups (Krance et al., 2019). It is therefore possible that whatever mechanism(s) of ACE-Is or ARBs might support their differential effects on Aβ accumulation in clinically normal people are less relevant in established AD. A recent study found that activity in the N-terminal catalytic domain of ACE-1 was approximately 50% lower in AD (Al Mulhim et al., 2019). Thus, it is possible that a difference between ACE-Is and ARBs was not observed in AD/MCI due to changes in the RAS system and its interactions with the amyloid cascade.

4.3. *Interactions with* APOE *carrier status*

The *APOE* allele is the strongest genetic risk factor for AD (Di Battista et al., 2016), and it was present in 60% of the AD/MCI group versus 32% of the cognitively normal group in this study. In the current analyses, *APOE* genotype was identified as an effect modifier, such that ARBs were associated with slower amyloid

accumulation among ε4 allele non-carriers compared to ε4 carriers. The finding suggests a possible explanation for the lack of an association between ACE-I versus ARB use and amyloid accumulation in Aβ+ AD/MCI, due to their increased prevalence of *APOE* ε4.

The reason for effect modification by *APOE* ε4 is unclear; it is possible that the molecular mechanisms underlying possible "benefits" of ARBs depend on the function of *APOE*, or that they are specifically nullified by the ε4 protein variant. The inhibitory effect of ACE-Is on the N-terminus of the ACE-1 enzyme may be lower in ε4 carriers (Qiu et al., 2014), thus the ε4 variant may nullify the hypothesized amyloidogenic effect of ACE-Is. As speculated above, it is possible that ACE-Is versus ARBs may be more relevant to Aβ accumulation below a certain Aβ threshold. Recent work by Burnham et al. (2020) found that *APOE* ε4 non-carriers reached an abnormal threshold for Aβ at an average age of 63, compared to 78 for ε4 carriers.

The largest statistically significant differences between ARB and ACE-I use were seen in cognitively normal people not carrying an *APOE* ε4 allele, where ARBs were associated with significantly less amyloid accumulation over time than ACE-Is. Cognitively normal *APOE* ε4 carriers using an ARB also showed numerically less amyloid accumulation over time than those using an ACE-I; although the effects globally and sub-regionally were of similar magnitude, they did not reach significance. Ultimately, this suggests that larger studies would be needed to determine if *APOE* carrier status modifies the treatment effects of ACE-Is versus ARBs on amyloid accumulation in clinically normal people, where the findings could have implications for AD prevention.

4.4. Study limitations and future directions

Strengths of this study include the use of longitudinal PET data, allowing assessment of relationships over time, biomarker confirmation of AD/MCI diagnoses, and statistical methodology (e.g., inverse-probability weighting) implemented to reduce possible confounding by indication; however, as this was an observational study, medication exposures were not randomized, and the analyses were largely exploratory. Further limitations must also be acknowledged, including sample size. For instance, the number of clinically normal people carrying an *APOE* ε4 allele was relatively small; given significant differences between ACE-Is and ARBs observed in this group, specifically in those not carrying an *APOE* ε4 allele, larger studies examining clinically normal people over time are needed (Rabin et al., 2019a). Although the properties of the different drugs to cross the blood-brain-barrier might be relevant, the available sample was too small to investigate subgroups of blood-brain-barrier-penetrating versus non-penetrating drugs. Dosing information and duration of prior exposure were incomplete in the dataset and therefore they were not included in the models. Additionally, the present observations do not speak specifically to the previously proposed effects of ACE-1 inhibition on amyloid metabolism, and they do not preclude the possibility that the relationship may be indirect, mediated by another process. For instance, tau and amyloid biomarkers appear to cascade in early stages of AD development (Krance et al., 2019). Tau PET was not sufficient in this sample to model, but other studies have found effects of ARBs on CSF tau (Nation et al., 2016). Given interactions between amyloid and vascular risk factors on tau (Rabin et al., 2019b), further mechanistic insight might be gained from examining possible differences in regional tau accumulation between ACE-Is and ARBs. Although the results are consistent with animal studies, they do not specify whether the effects of ACE-Is versus ARBs may be due to differences in processes related to amyloid synthesis, metabolism, deposition, or clearance specifically.

Genetic factors beyond *APOE* might also identify people who respond differently to an ARB versus an ACE-I, and in that regard, polygenic risk scores for AD (Tan et al., 2019), or genetic variants in the RAS system (Oliveira et al., 2018), might be investigated. Specifically, an insertion/deletion polymorphism in the gene encoding ACE-1 has been associated with higher levels of ACE-1 in both the periphery (Rigat et al., 1990) and in the brain (Miners et al., 2009), and variation in ACE genotypes may influence ACE-I response (Scharplatz et al., 2005). Thus, it would be pertinent for future studies to consider the potential role of ACE-1 genotype in moderating the effects of ARBs and ACE-Is on the brain.

5. Conclusions

The present findings add clinical evidence that ARBs relative to ACE-Is are associated with less Aβ accumulation over time in cognitively normal older adults, consistent with previously described differences in markers of neurodegeneration and cognition. The lack of difference in Aβ accumulation among people with clinical AD/MCI, and the identified interaction with *APOE* carrier status, may further explain heterogeneity in associations between RAS-acting antihypertensives and cognition described previously, and might further help to identify target populations for individualized pharmacotherapy. Replication in larger longitudinal studies of cognitively normal people, and randomized controlled trials, would be needed to ascertain potential clinical benefit of these findings.

Disclosure statement

The authors report no conflicts of interest.

CRediT authorship contribution statement

Michael Ouk: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing. **Che-Yuan Wu:** Formal analysis, Investigation, Methodology, Software, Validation, Writing - review & editing. **Jennifer S. Rabin:** Conceptualization, Formal analysis, Supervision, Writing - review & editing. **Jodi D. Edwards:** Conceptualization, Formal analysis, Supervision, Writing - review & editing. **Joel Ramirez:** Conceptualization, Writing - review & editing. **Mario Masellis:** Writing - review & editing. **Richard H. Swartz:** Writing - review & editing. **Nathan Herrmann:** Conceptualization, Writing - review & editing. **Krista L. Lanctôt:** Conceptualization, Writing - review & editing. **Sandra E. Black:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing. **Walter Swardfager:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing - original draft, Writing - review & editing.

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Appendix A. Supplementary data

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References

Al Mulhim, N.S., Kehoe, P.G., Miners, J.S., 2019. Divergence in the activity of the N- and C- catalytic domains of ACE1 - implications for the role of the renin-angiotensin system in Alzheimer's disease. Acta Neuropathol. Commun. 7, 57.

Ashby, E.L., Miners, J.S., Kehoe, P.G., Love, S., 2016. Effects of hypertension and antihypertensive treatment on amyloid-β (Aβ) plaque load and Aβ-synthesizing and Aβ-degrading enzymes in frontal cortex. J. Alzheimer's Dis. 50, 1191–1203.

Barthold, D., Joyce, G., Wharton, W., Kehoe, P., Zissimopoulos, J., 2018. The association of multiple anti-hypertensive medication classes with Alzheimer's disease incidence across sex, race, and ethnicity. PLoS One 13, e0206705.

Bates, D., Mächler, M., Bolker, B., Walker, S., 2015. Fitting linear mixed-effects models using lme4. J. Stat. Softw. 1, 1–48.

Benson, S.C., Pershadsingh, H.A., Ho, C.I., Chittiboyina, A., Desai, P., Pravenac, M., Qi, N., Wang, J., Avery, M.A., Kurtz, T.W., 2004. Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARγ–modulating activity. Hypertension 43, 993–1002.

Bohlken, J., Jacob, L., Kostev, K., 2019. The relationship between the use of antihypertensive drugs and the incidence of dementia in general practices in Germany. J. Alzheimer's Dis. 70, 91–97.

Carnevale, D., Mascio, G., D'Andrea, I., Fardella, V., Bell, R.D., Branchi, I., Pallante, F., Zlokovic, B., Yan, S.S., Lembo, G., 2012. Hypertension induces brain β-amyloid accumulation, cognitive impairment, and memory deterioration through activation of receptor for advanced glycation end products in brain vasculature. Hypertens. (Dallas, Tex. 1979) 60, 188–197.

Chobanian, A.V., Bakris, G.L., Black, H.R., Cushman, W.C., Green, L.A., Izzo, J.L., Jones, D.W., Materson, B.J., Oparil, S., Wright, J.T., Roccella, E.J., the National High Blood Pressure Education Program Coordinating Committee, 2003. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 42, 1206–1252.

Danielyan, L., Klein, R., Hanson, L.R., Buadze, M., Schwab, M., Gleiter, C.H., Frey, W.H., 2010. Protective effects of intranasal Losartan in the APP/PS1 transgenic mouse model of Alzheimer disease. Rejuvenat. Res. 13, 195–201.

Di Battista, A.M., Heinsinger, N.M., Rebeck, G.W., 2016. Alzheimer's disease genetic risk factor APOE-ε4 also affects normal brain function. Curr. Alzheimer Res. 13, 1200–1207.

Ding, J., Davis-Plourde, K.L., Sedaghat, S., Tully, P.J., Wang, W., Phillips, C., Pase, M.P., Himali, J.J., Gwen Windham, B., Griswold, M., Gottesman, R., Mosley, T.H., White, L., Guðnason, V., Debette, S., Beiser, A.S., Seshadri, S., Ikram, M.A., Meirelles, O., Tzourio, C., Launer, L.J., 2020. Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies. Lancet Neurol. 19, 61–70.

Drews, H.J., Yenkoyan, K., Lourhmati, A., Buadze, M., Kabisch, D., Verleysdonk, S., Petschak, S., Beer-Hammer, S., Davtyan, T., Frey, W.H., Gleiter, C.H., Schwab, M., Danielyan, L., 2019. Intranasal Losartan decreases perivascular beta amyloid, inflammation, and the decline of neurogenesis in hypertensive rats. Neurotherapeutics 16, 725–740.

Duron, E., Rigaud, A.-S., Dubail, D., Mehrabian, S., Latour, F., Seux, M.-L., Hanon, O., 2009. Effects of antihypertensive therapy on cognitive decline in Alzheimer's disease. Am. J. Hypertens. 22, 1020–1024.

Edwards, J.D., Ramirez, J., Callahan, B.L., Tobe, S.W., Oh, P., Berezuk, C., Lanctôt, K., Swardfager, W., Nestor, S., Kiss, A., Strother, S., Black, S.E., 2017. Antihypertensive treatment is associated with MRI-derived markers of neurodegeneration and impaired cognition: a propensity-weighted cohort study. J. Alzheimer's Dis. 59, 1113–1122.

Evans, C.E., Miners, J.S., Piva, G., Willis, C.L., Heard, D.M., Kidd, E.J., Good, M.A., Kehoe, P.G., 2020. ACE2 activation protects against cognitive decline and reduces amyloid pathology in the Tg2576 mouse model of Alzheimer's disease. Acta Neuropathol. 139, 485–502.

Fournier, A., Oprisiu-Fournier, R., Serot, J.-M., Godefroy, O., Achard, J.-M., Faure, S., Mazouz, H., Temmar, M., Albu, A., Bordet, R., Hanon, O., Gueyffier, F., Wang, J., Black, S., Sato, N., 2009. Prevention of dementia by antihypertensive drugs: how AT1-receptor-blockers and dihydropyridines better prevent dementia in hypertensive patients than thiazides and ACE-inhibitors. Expert Rev. Neurother. 9, 1413–1431.

Furuhashi, M., Moniwa, N., Mita, T., Fuseya, T., Ishimura, S., Ohno, K., Shibata, S., Tanaka, M., Watanabe, Y., Akasaka, H., Ohnishi, H., Yoshida, H., Takizawa, H., Saitoh, S., Ura, N., Shimamoto, K., Miura, T., 2015. Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker. Am. J. Hypertens. 28, 15–21.

Gelber, R.P., Ross, G.W., Petrovitch, H., Masaki, K.H., Launer, L.J., White, L.R., 2013. Antihypertensive medication use and risk of cognitive impairment: the Honolulu-Asia Aging Study. Neurology 81, 888–895.

Glodzik, L., Rusinek, H., Kamer, A., Pirraglia, E., Tsui, W., Mosconi, L., Li, Y., McHugh, P., Murray, J., Williams, S., Osorio, R.S., Randall, C., Butler, T., Deshpande, A., Vallabhajolusa, S., de Leon, M., 2016. Effects of vascular risk factors, statins, and antihypertensive drugs on PiB deposition in cognitively normal subjects. Alzheimer's Dement. (Amsterdam, Netherlands) 2, 95–104.

Goh, K.L., Bhaskaran, K., Minassian, C., Evans, S.J.W., Smeeth, L., Douglas, I.J., 2015. Angiotensin receptor blockers and risk of dementia: cohort study in UK Clinical Practice Research Datalink. Br. J. Clin. Pharmacol. 79, 337–350.

Gómez-Rubio, V., 2017. ggplot2 - Elegant graphics for data analysis (second ed.). J. Stat. Software, 1. Springer-Verlag, New York. B. Rev. 2.

Greicius, M.D., Srivastava, G., Reiss, A.L., Menon, V., 2004. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc. Natl. Acad. Sci. U. S. A. 101, 4637–4642.

Grimm, M., Mett, J., Stahlmann, C., Haupenthal, V., Zimmer, V., Hartmann, T., 2013. Neprilysin and Aβ clearance: impact of the APP intracellular domain in NEP regulation and implications in Alzheimer's disease. Front. Aging Neurosci. 5, 1–27. Article 98.

Grothe, M.J., Barthel, H., Sepulcre, J., Dyrba, M., Sabri, O., Teipel, S.J., Initiative, A.D.N., 2017. In vivo staging of regional amyloid deposition. Neurology 89, 2031–2038.

Hajjar, I., Brown, L., Mack, W.J., Chui, H., 2012. Impact of angiotensin receptor blockers on Alzheimer disease neuropathology in a large brain autopsy series. Arch. Neurol. 69, 1632–1638.

Hemming, M.L., Selkoe, D.J., 2005. Amyloid beta-protein is degraded by cellular angiotensin-converting enzyme (ACE) and elevated by an ACE inhibitor. J. Biol. Chem. 280, 37644–37650.

Ho, J.K., Nation, D.A., 2017. Memory is preserved in older adults taking AT1 receptor blockers. Alzheimer's Res. Ther. 9, 1–14.

Jack, C.R., Wiste, H.J., Lesnick, T.G., Weigand, S.D., Knopman, D.S., Vemuri, P., Pankratz, V.S., Senjem, M.L., Gunter, J.L., Mielke, M.M., Lowe, V.J., Boeve, B.F., Petersen, R.C., 2013. Brain β-amyloid load approaches a plateau. Neurology 80, 890. LP – 896.

Kehoe, P.G., 2018. The coming of age of the angiotensin hypothesis in Alzheimer's disease: progress toward disease prevention and treatment? J. Alzheimers. Dis. 62, 1443–1466.

Kennelly, S.P., Lawlor, B.A., Kenny, R.A., 2009. Blood pressure and dementia—a comprehensive review. Ther. Adv. Neurol. Disord. 2, 241–260.

Krance, S.H., Cogo-Moreira, H., Rabin, J.S., Black, S.E., Swardfager, W., Initiative, A.D.N., 2019. Reciprocal predictive relationships between amyloid and tau biomarkers in Alzheimer's disease progression: an empirical model. J. Neurosci. 39, 7428–7437.

Landau, S.M., Breault, C., Joshi, A.D., Pontecorvo, M., Mathis, C.A., Jagust, W.J., Mintun, M.A., Initiative, A.D.N., 2013. Amyloid-β imaging with Pittsburgh compound B and florbetapir: comparing radiotracers and quantification methods. J. Nucl. Med. 54, 70–77.

Landau, S.M., Fero, A., Baker, S.L., Koeppe, R., Mintun, M., Chen, K., Reiman, E.M., Jagust, W.J., 2015. Measurement of longitudinal β-amyloid change with 18F-florbetapir PET and standardized uptake value ratios. J. Nucl. Med. 56, 567–574.

Lawlor, B., Segurado, R., Kennelly, S., Olde Rikkert, M.G.M., Howard, R., Pasquier, F., Börjesson-Hanson, A., Tsolaki, M., Lucca, U., Molloy, D.W., Coen, R., Riepe, M.W., Kálmán, J., Kenny, R.A., Cregg, F., O'Dwyer, S., Walsh, C., Adams, J., Banzi, R., Breuilh, L., Daly, L., Hendrix, S., Aisen, P., Gaynor, S., Sheikhi, A., Taekema, D.G., Verhey, F.R., Nemni, R., Nobili, F., Franceschi, M., Frisoni, G., Zanetti, O., Konsta, A., Anastasios, O., Nenopoulou, S., Tsolaki-Tagaraki, F., Pakaski, M., Dereeper, O., de la Sayette, V., Sénéchal, O., Lavenu, I., Devendeville, A., Calais, G., Crawford, F., Mullan, M., Group, N.S., 2018. Nilvadipine in mild to moderate Alzheimer disease: a randomised controlled trial. PLoS Med. 15, e1002660.

Li, E.C.K., Heran, B.S., Wright, J.M., 2014. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. Cochrane Database Syst. Rev. (8), 1–49.

Li, N.-C., Lee, A., Whitmer, R.A., Kivipelto, M., Lawler, E., Kazis, L.E., Wolozin, B., 2010. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. BMJ 340, b5465.

Liu, C.-C., Zhao, N., Fu, Y., Wang, N., Linares, C., Tsai, C.-W., Bu, G., 2017. ApoE4 accelerates early seeding of amyloid pathology. Neuron 96, 1024–1032.e3.

Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S.G., Huntley, J., Ames, D., Ballard, C., Banerjee, S., Burns, A., Cohen-Mansfield, J., Cooper, C., Fox, N., Gitlin, L.N., Howard, R., Kales, H.C., Larson, E.B., Ritchie, K., Rockwood, K., Sampson, E.L., Samus, Q., Schneider, L.S., Selbæk, G., Teri, L., Mukadam, N., 2017. Dementia prevention, intervention, and care. Lancet 390, 2673–2734.

Mattsson, N., Palmqvist, S., Stomrud, E., Vogel, J., Hansson, O., 2019. Staging β-amyloid pathology with amyloid positron emission tomography. JAMA Neurol. 76, 1319–1329.

Mevel, K., Chételat, G., Eustache, F., Desgranges, B., 2011. The default mode network in healthy aging and Alzheimer's disease. Int. J. Alzheimer's Dis. 2011, 535816.

Miners, S., Ashby, E., Baig, S., Harrison, R., Tayler, H., Speedy, E., Prince, J.A., Love, S., Kehoe, P.G., 2009. Angiotensin-converting enzyme levels and activity in Alzheimer's disease: differences in brain and CSF ACE and association with ACE1 genotypes. Am. J. Transl. Res. 1, 163–177.

Mogi, M., Li, J.-M., Tsukuda, K., Iwanami, J., Min, L.-J., Sakata, A., Fujita, T., Iwai, M., Horiuchi, M., 2008. Telmisartan prevented cognitive decline partly due to PPAR-γ activation. Biochem. Biophys. Res. Commun. 375, 446–449.

Moran, C., Xie, K., Poh, S., Chew, S., Beare, R., Wang, W., Callisaya, M., Srikanth, V., 2019. Observational study of brain atrophy and cognitive decline comparing a sample of community-dwelling people taking angiotensin converting enzyme inhibitors and angiotensin receptor blockers over time. J. Alzheimer's Dis. 68, 1479–1488.

Nation, D.A., Ho, J., Yew, B., Initiative, A.D.N., 2016. Older adults taking AT1-receptor blockers exhibit reduced cerebral amyloid retention. J. Alzheimers. Dis. 50, 779–789.

Oba, R., Igarashi, A., Kamata, M., Nagata, K., Takano, S., Nakagawa, H., 2005. The N-terminal active centre of human angiotensin-converting enzyme degrades Alzheimer amyloid β-peptide. Eur. J. Neurosci. 21, 733–740.

Oliveira, F.F., de, Chen, E.S, Bertolucci, M.C.S, P.H.F, 2018. Pharmacogenetics of angiotensin-converting enzyme inhibitors in patients with Alzheimer's disease dementia. Curr. Alzheimer Res. 15, 386–398.

Palmqvist, S., Schöll, M., Strandberg, O., Mattsson, N., Stomrud, E., Zetterberg, H., Blennow, K., Landau, S., Jagust, W., Hansson, O., 2017. Earliest accumulation of β-

amyloid occurs within the default-mode network and concurrently affects brain connectivity. Nat. Commun. 8, 1214.
Paz Ocaranza, M., Riquelme, J.A., García, L., Jalil, J.E., Chiong, M., Santos, R.A.S., Lavandero, S., 2020. Counter-regulatory renin-angiotensin system in cardiovascular disease. Nat. Rev. Cardiol. 17, 116–129.
Perrotta, M., Lembo, G., Carnevale, D., 2016. Hypertension and dementia: epidemiological and experimental evidence revealing a detrimental relationship. Int. J. Mol. Sci. 17, 347.
Peters, R., Yasar, S., Anderson, C.S., Andrews, S., Antikainen, R., Arima, H., Beckett, N., Beer, J.C., Bertens, A.S., Booth, A., van Boxtel, M., Brayne, C., Brodaty, H., Carlson, M.C., Chalmers, J., Corrada, M., DeKosky, S., Derby, C., Dixon, R.A., Forette, F., Ganguli, M., van Gool, W.A., Guaita, A., Hever, A.M., Hogan, D.B., Jagger, C., Katz, M., Kawas, C., Kehoe, P.G., Keinanen-Kiukaanniemi, S., Kenny, R.A., Köhler, S., Kunutsor, S.K., Laukkanen, J., Maxwell, C., McFall, G.P., van Middelaar, T., Moll van Charante, E.P., Ng, T.-P., Peters, J., Rawtaer, I., Richard, E., Rockwood, K., Rydén, L., Sachdev, P.S., Skoog, I., Skoog, J., Staessen, J.A., Stephan, B.C.M., Sebert, S., Thijs, L., Trompet, S., Tully, P.J., Tzourio, C., Vaccaro, R., Vaaramo, E., Walsh, E., Warwick, J., Anstey, K.J., 2020. Investigation of antihypertensive class, dementia, and cognitive decline. Neurology 94, e267. LP-e281.
Qiu, W.W.Q., Lai, A., Mon, T., Mwamburi, M., Taylor, W., Rosenzweig, J., Kowall, N., Stern, R., Zhu, H., Steffens, D.C., 2014. Angiotensin converting enzyme inhibitors and Alzheimer disease in the presence of the apolipoprotein E4 allele. Am. J. Geriatr. Psychiatry 22, 177–185.
Rabin, J.S., Perea, R.D., Buckley, R.F., Johnson, K.A., Sperling, R.A., Hedden, T., 2019a. Synergism between fornix microstructure and beta amyloid accelerates memory decline in clinically normal older adults. Neurobiol. Aging 81, 38–46.
Rabin, J.S., Yang, H.-S., Schultz, A.P., Hanseeuw, B.J., Hedden, T., Viswanathan, A., Gatchel, J.R., Marshall, G.A., Kilpatrick, E., Klein, H., Rao, V., Buckley, R.F., Yau, W.-Y.W., Kirn, D.R., Rentz, D.M., Johnson, K.A., Sperling, R.A., Chhatwal, J.P., 2019b. Vascular risk and β-amyloid are synergistically associated with cortical tau. Ann. Neurol. 85, 272–279.
Rigat, B., Hubert, C., Alhenc-Gelas, F., Cambien, F., Corvol, P., Soubrier, F., 1990. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J. Clin. Invest. 86, 1343–1346.
Rodgers, J.E., Patterson, J.H., 2001. Angiotensin II-receptor blockers: clinical relevance and therapeutic role. Am. J. Heal. Pharm. 58, 671–683.
Scharplatz, M., Puhan, M.A., Steurer, J., Perna, A., Bachmann, L.M., 2005. Does the angiotensin-converting enzyme (ACE) gene insertion/deletion polymorphism modify the response to ACE inhibitor therapy? A systematic review. Curr. Control Trials Cardiovasc. Med. 6, 16.
Shuko, T., Naoyuki, S., Daisuke, T., Hitomi, K., Mitsuru, S., Kazue, N., Masanobu, K., Toshio, O., Hiromi, R., Ryuichi, M., 2009. Angiotensin receptor blocker prevented β-amyloid-induced cognitive impairment associated with recovery of neurovascular coupling. Hypertension 54, 1345–1352.
Skoog, I., Nilsson, L., Persson, G., Lernfelt, B., Landahl, S., Palmertz, B., Andreasson, L.-A., Odén, A., Svanborg, A., 1996. 15-year longitudinal study of blood pressure and dementia. Lancet 347, 1141–1145.
Tan, C.H., Bonham, L.W., Fan, C.C., Mormino, E.C., Sugrue, L.P., Broce, I.J., Hess, C.P., Yokoyama, J.S., Rabinovici, G.D., Miller, B.L., Yaffe, K., Schellenberg, G.D., Kauppi, K., Holland, D., McEvoy, L.K., Kukull, W.A., Tosun, D., Weiner, M.W., Sperling, R.A., Bennett, D.A., Hyman, B.T., Andreassen, O.A., Dale, A.M., Desikan, R.S., Initiative, A.D.N., 2019. Polygenic hazard score, amyloid deposition and Alzheimer's neurodegeneration. Brain 142, 460–470.
Tublin, J.M., Adelstein, J.M., del Monte, F., Combs, C.K., Wold, L.E., 2019. Getting to the heart of Alzheimer disease. Circ. Res. 124, 142–149.
Vaduganathan, M., Vardeny, O., Michel, T., McMurray, J.J.V., Pfeffer, M.A., Solomon, S.D., 2020. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. N. Engl. J. Med. 382, 1653–1659.
van der Wal, W.M., Geskus, R.B., 2011. ipw: an R package for inverse probability weighting. J. Stat. Softw. 1, 1–23.
Verghese, P.B., Castellano, J.M., Garai, K., Wang, Y., Jiang, H., Shah, A., Bu, G., Frieden, C., Holtzman, D.M., 2013. ApoE influences amyloid-β (Aβ) clearance despite minimal apoE/Aβ association in physiological conditions. Proc. Natl. Acad. Sci. U. S. A. 110, E1807–E1816.
Villemagne, V.L., Burnham, S., Bourgeat, P., Brown, B., Ellis, K.A., Salvado, O., Szoeke, C., Macaulay, S.L., Martins, R., Maruff, P., Ames, D., Rowe, C.C., Masters, C.L., 2013. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol. 12, 357–367.
Walker, V.M., Kehoe, P.G., Martin, R.M., Davies, N.M., 2019. Repurposing antihypertensive drugs for the prevention of Alzheimer's disease: a Mendelian randomization study. Int. J. Epidemiol. 49, 1132–1140.
Wang, J., Ho, L., Chen, L., Zhao, Z., Zhao, W., Qian, X., Humala, N., Seror, I., Bartholomew, S., Rosendorff, C., Pasinetti, G.M., 2007. Valsartan lowers brain beta-amyloid protein levels and improves spatial learning in a mouse model of Alzheimer disease. J. Clin. Invest. 117, 3393–3402.
Xu, G., Bai, F., Lin, X., Wang, Q., Wu, Q., Sun, S., Jiang, C., Liang, Q., Gao, B., 2017. Association between antihypertensive drug use and the incidence of cognitive decline and dementia: a meta-analysis of prospective cohort studies. Biomed. Res. Int. 2017, 4368474.
Yasar, S., Xia, J., Yao, W., Furberg, C.D., Xue, Q.-L., Mercado, C.I., Fitzpatrick, A.L., Fried, L.P., Kawas, C.H., Sink, K.M., Williamson, J.D., DeKosky, S.T., Carlson, M.C., Investigators, G.E. of M. (GEM) S., 2013. Antihypertensive drugs decrease risk of Alzheimer disease: Ginkgo evaluation of memory study. Neurology 81, 896–903.
Zou, K., Yamaguchi, H., Akatsu, H., Sakamoto, T., Ko, M., Mizoguchi, K., Gong, J.-S., Yu, W., Yamamoto, T., Kosaka, K., Yanagisawa, K., Michikawa, M., 2007. Angiotensin-converting enzyme converts amyloid β-protein 1–42 (Aβ1–42) to Aβ1–40, and its inhibition enhances brain Aβ deposition. J. Neurosci. 27, 8628. LP – 8635.