Neurofibrillary Tangles and Conversion to Mild Cognitive Impairment with Certain Antihypertensives

Whitney Wharton[a,b,*], Liping Zhao[c], Kyle Steenland[d], Felicia C. Goldstein[a], Julie A. Schneider[e,f],
Lisa L. Barnes[f], Marla Gearing[a] and Sevil Yasar[g]
[a]*Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA*
[b]*Emory University, School of Nursing, Atlanta, GA, USA*
[c]*Emory University Department of Biostatistics and Bioinformatics, School of Public Health, Atlanta, GA, USA*
[d]*Rollins School of Public Health, Biostatistics and Bioinformatics, Atlanta, GA, USA*
[e]*Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA*
[f]*Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA*
[g]*Johns Hopkins University School of Medicine, Department of Medicine, Baltimore, MD, USA*

Abstract.

Background: Individuals taking renin angiotensin system (RAS) acting antihypertensives exhibit slower cognitive decline and are less likely to progress from mild cognitive impairment (MCI) to Alzheimer's disease (AD), but the mechanism remains unclear.

Objective: We tested the hypothesis that individuals taking RAS acting antihypertensives exhibit less AD-related neuropathology and slower disease progression than individuals taking non-RAS acting antihypertensives.

Method: Participants included 83 individuals with MCI who were taking an antihypertensive at baseline, had at least two follow-up visits, and had postmortem neuropathological data. Participants were old ($M = 83.1$ years), 32% male, well educated ($M = 15.7$ years), and 9.2% Black.

Results: RAS medication users ($N = 38$) were less likely to progress to AD than non-RAS users ($N = 45$). RAS users exhibited fewer neurofibrillary tangles than non-RAS users in the hippocampal CA1 region ($p < 0.01$), entorhinal cortex ($p = 0.03$), and the angular gyrus, inferior temporal, mid-frontal cortex, and superior frontal ($p = 0.01$).

Conclusion: Prevention or clearance of neurofibrillary tangles represents a mechanism by which RAS medications may slow disease progression.

Keywords: Alzheimer's disease, blood pressure, hypertension, mild cognitive impairment, neuropathology, prevention, renin angiotensin system, tau

INTRODUCTION

The increasing age of the population of the United States and other developed countries is accompanied by an increasing prevalence of dementia, which doubles every decade over age 65 [1]. There is currently no effective treatment available, thus identifying new and potentially effective approaches to prevention and/or treatment is critical. Repurposing medications generally recognized as safe, and showing promise in Alzheimer's disease (AD) could shorten the time to provide urgently needed treatment options.

The renin angiotensin system (RAS) generates bioactive angiotensin peptides with a wide range of

*Correspondence to: Whitney Wharton, PhD, Assistant Professor, Emory University, Department of Neurology, 12 Executive Park Dr NE, Atlanta, GA, USA. E-mail: w.wharton@emory.edu.

biological activities and plays a key role in blood pressure (BP) regulation. There is increasing evidence about the possible involvement of the RAS in the pathogenesis of AD either independently, or in combination with BP control, that has effects on vascular function and modulation of amyloid and tau metabolism [2–9].

Epidemiological studies suggest that antihypertensive medications (AHM) may have a protective effect in addition to, or independent of, their ability to control BP, and this effect may be specific to the class of drugs to which they belong. Furthermore, epidemiological studies also suggest that AHM acting via the RAS, such as angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin II type 1 receptor blockers (AT1RBs), protect against risk of AD by 20–70% [10, 11]. We recently reported, that participants with mild cognitive impairment (MCI) using RAS-AHM were less likely to convert to AD and also had slower cognitive and functional decline [12].

RAS-AHM has been shown to lower amyloid-β (Aβ) and prevent abnormal hyperphosphorylation of tau [13, 14], which are the pathological hallmarks of AD [15–17].

The objective of this study was to confirm that RAS-AHM are related to slower conversion from MCI to AD than non RAS-AHM, and determine possible neuropathological mechanisms driving this phenomenon.

METHODS

Participants

Data from the Rush Alzheimer's Disease Core Center (Rush ADCC) was used for the present study. Data included diagnostic, clinical, and neuropathological information from three well-characterized Rush University cohorts including 1) The Rush Clinical Core, 2) The Religious Orders Study, and 3) the Rush Memory and Aging Project. Standardized protocols for these studies have been described elsewhere [18, 19]. The three studies follow virtually identical protocols, including recruitment, and demographic, clinical, and biospecimen collection.

The Religious Orders Study began enrolling in 1994 from across the United States. Of the 1,344 participants enrolled, 732 died, of which 675 underwent autopsy. 640 participants had complete neuropathologic data thus were included into our study [19]. The Rush Memory and Aging Project started to enroll in 1997 from the Chicago area. Of the 1,865 participants

enrolled, 820 died, of which 666 underwent autopsy. 627 participants had complete neuropathologic data thus were included into our study [20].

Data was current as of March 2016 and all participants had two or more annual visits. Participants had annual diagnostic assessments, as well as medical history, medication information, physical examination, and neuropsychological testing.

We included only participants with MCI diagnosis at baseline, who reported AHM use at all visits and who completed postmortem neuropathological exam. MCI diagnosis was based on NIA-Alzheimer's Association diagnostic guidelines [21], since participants with MCI are at high risk for developing AD, and it has been shown that delaying onset of AD by 1 year could result in 9 million fewer AD cases by 2050 [22].

Clinical diagnosis of mild cognitive impairment and dementia

Written consent was obtained for all subjects and the Rush Institutional Review Board approved the study. Clinical and diagnostic information for participants in the three cohorts was assessed annually using NINDS-ADRDA criteria [23]. Final diagnosis was determined using the last clinical data available before death by an experienced member of the Rush ADCC with expertise in dementia, and who was blinded to prior clinical diagnoses.

Medication classification

Normotensive and untreated hypertensive participants (BP reading ≥140 mmHg systolic or ≥90 mmHg diastolic) at baseline were excluded. AHM were classified into 5 groups: angiotensin converting enzyme inhibitors (ACE-I) (benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril, trandolapril), angiotensin receptor blockers (A2RB) (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan), beta blockers (acebutolol, atenolol, bisoprolol, carvedilol, labetolol, metoprolol, nadolol, pindolol, propranolol), calcium channel blockers (amlodipine, felodipine, nifedipine, nisolodipine, verapamil), and diuretics (bumetanide, furosemide, hydrochlorothiazide, indapamide, metolazone, spironolactone, triamterene, torsemide). Participants reporting use of ACE-I and/or A2RB during each visit were assigned to RAS acting medications (RAS-AHM) group, while those taking other AHM (beta blockers and/or calcium channel blockers and/or diuretics) during each

visit were assigned to non RAS medication group (non RAS-AHM). Participants taking at any visit both RAS-AHM and non RAS-AHM were assigned in the RAS-AHM group, as long as RAS-AHM use was consistent across all visits.

Neuropathologic data

Rush neuropathologists, blind to clinical diagnosis, conducted a systematic neuropathological assessment of each autopsied brain as described elsewhere [24]. In summary, standardized gross and histological assessments were conducted for common age-related diseases, including but not limited to AD, cerebrovascular disease and Lewy body dementia.

AD-related neuropathological data was collected, including 1) brain weight, 2) high/intermediate probability of AD based on NIA Reagan score, 3) overall amyloid score, 4) diffuse plaques, 5) arteriolosclerosis (0–3), 6) Braak score, 7) NFT total count, and 8) NFT count in specific brain regions including the hippocampus CA1, entorhinal cortex, and the average number of tangles in the combined regions including angular gyrus, inferior temporal, mid-frontal cortex and superior frontal. Braak, CERAD, cerebral infarcts, and arteriolosclerosis measures are scored semi-quantitatively.

Statistical analyses

Because the primary outcome of this study was to determine rate of progression from MCI to AD, we used Cox proportional hazards model (SAS PROC PHREG) to estimate the effect of RAS-AHM. We adjusted for baseline age, sex, race, education, systolic BP, and depression in all models. Diabetes mellitus was not included in this analysis because none of the participants with diabetes mellitus converted. The time variable was time to conversion to AD or follow-up time after baseline. The first variable of interest was RAS-AHM use versus non RAS-AHM use over time. Hazard ratios (HRs) with their 95% confidence intervals (CIs) were calculated from the model. We tested the proportional hazards assumption by including interaction terms between time and predictors in the models and examining all the time dependent covariates.

For our secondary outcome to measure change in AD-related neuropathology, we made log transformation for brain weight and average number of tangles, and square root transformation for NFTs,

overall amyloid burden, average diffuse plaques, tangle count in hippocampus CA1 and entorhinal cortex to approximate a normal distribution since neuropathological scores including all four NFT count variables and brain weight did not follow a normal distribution. The outcomes were analyzed with multiple linear regression models (SAS PROC LMG), and percent of difference or difference of least square means between RAS-AHM users and non RAS-AHM users were calculated. Because the other neuropathological outcomes, including probability of AD based on Reagan score (two categories), Braak score (three categories), arteriolosclerosis (four categories), and CERAD neuropathologic diagnosis of AD (4 categories), were discrete with multiple categories staging dementia severity, multinomial logistic regression models (SAS PROC LOGISTIC) were applied and odds ratios (ORs) were computed. All models were adjusted for baseline age, sex, race, education, systolic BP, diabetes, and depression.

Data availability statement

Anonymized data can be shared by request from any qualified investigator.

RESULTS

Participants

Figure 1 shows the participants included in the analyses. Of the 937 participants with a baseline diagnosis of MCI, 388 reported use of BP medication and 146 reported no use of an antihypertensive during any of the visits and were therefore excluded. Of participants reporting AHM use at all visits, 132 were always on a RAS-AHM and 107 were on non RAS-AHM. For the present analyses, participants included 83 individuals with MCI at baseline who were taking an AHM at baseline and through follow-up, and who had postmortem neuropathological data (RAS-AHM $N = 38$; non RAS-AHM $N = 45$). In the non RAS-AHM group, 12 were taking a calcium channel blocker alone, 10 were taking a beta blocker alone, seven were taking a diuretic alone and 16 were taking a combination of any of these medications. In the RAS-AHM group, 29 were taking an ACE-I and nine were taking an A2RB.

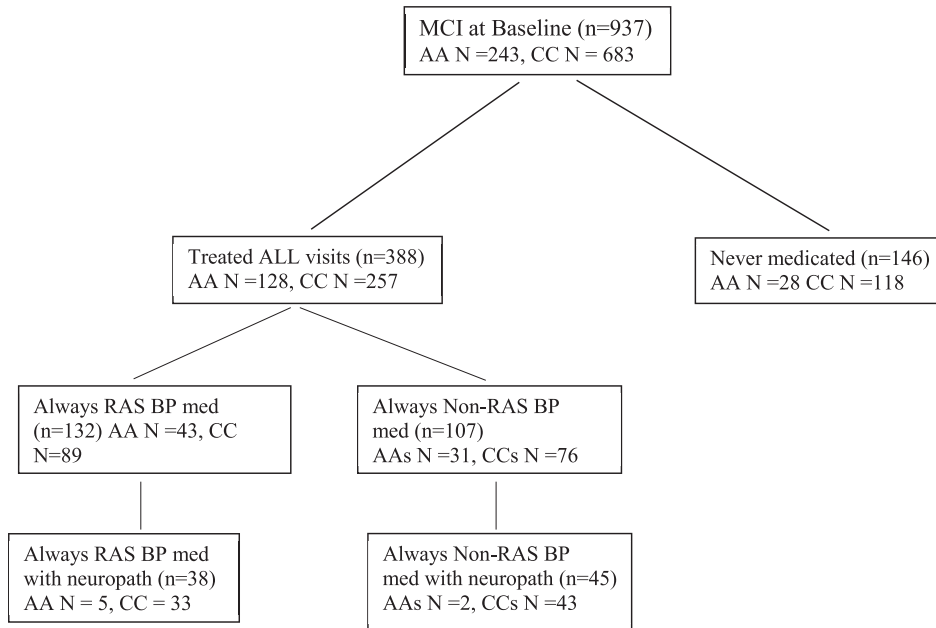Table 1 lists baseline demographic and clinical variables by RAS user group.

Fig. 1. Consort diagram of participants included in the present study. Note: Analyses include only participants treated for hypertension at each study visit and had neuropathological data. Participants with high blood pressure but not on a medication, as well as normotensives were not included. AA, African American; CC, Caucasian; RAS, renin-angiotensin system; BP, blood pressure. *Eleven individuals did not report race at Baseline.

Table 1
Baseline demographic and vascular measures for RAS users and RAS non-users
diagnosed with MCI at baseline and treated with an antihypertensive medication

Variable	RAS Users N = 38	RAS non-users N = 45	p
Age (y)	82.6 ± 7.2	83.7 ± 5.9	p = 0.43
Education (y)	16.0 ± 3.6	15.4 ± 3.1	p = 0.38
Race (% Black)	13.9%	4.4%	p = 0.13
Sex (% Male)	45%	20%	p = 0.02
Systolic (mmHg)	138 ± 16.9	139 ± 21.4	p = 0.75
Diastolic (mmHg)	72.7 ± 12.5	71.2 ± 10.7	p = 0.57
Body mass index	27.0 ± 5.6	26.4 ± 4.9	p = 0.64
Diabetes (%)	24%	0.4%	p = 0.01
ApoE4 positive (%)	22.9%	33.3%	p = 0.30
Number of depressive symptoms	1 (0 – 2)	1 (0 – 3)	p = 0.23
Ever Smoker (%)	32%	22%	p = 0.16
AD Medication User (%)	8%	2%	p = 0.23
Mini-Mental State Examination	26.9 ± 2.4	26.8 ± 2.2	p = 0.87
FU time in years	4.2 ± 3.0	4.3 ± 2.8	p = 0.84

*FU time, Follow up until time to conversion or last follow-up visit.

There were no group differences on demographic variables except sex, such that the RAS user group included more males (44.7% versus 20.0%). Participants were older adults ($M = 83.2$ years), well educated ($M = 15.7$ years), 8.5% self-identified as Black, and 4.8% were taking a medication indicated for AD. Groups did not differ in percent of individuals who were ApoE4 positive (28.8%) or baseline Mini-Mental State Examination score ($M = 26.9$), while there were no group differences in BP ($M = 138/72$ mmHg), HDL ($M = 60$ mg/dL), or LDL ($M = 102$ mg/dL). RAS-AHM users were more likely to be diabetic than non RAS-AHM users ($p = 0.01$). There was no difference between

Table 2
Conversion Rate and Neuropathological Data by RAS medication group

Conversion Rate and Neuropathological Variable	Unadjusted			Adjusted*	
	RAS-AHM ($n = 38$)	non RAS-AHM Medication ($n = 45$)	p	RAS versus non-RAS	p
Conversion to AD/dementia	3 (7.9)	11 (24.4)	0.0185	0.12 (0.02–0.80)	0.0285
Square root of brain weight	33.6 ± 2.21	33.8 ± 1.84	0.65	−1.85 ± 0.82	0.0338
High/intermediate probability of AD based on NIA Reagan score	23 (63.9)	31 (72.1)	0.43	0.84 (0.27–2.66)	0.77
Square root of overall amyloid level	1.4 ± 1.3	1.7 ± 1.1	0.23	−0.73 ± 0.39	0.07
Square root of diffuse plaques	0.65 ± 0.50	0.85 ± 0.50	0.09	−0.47 ± 0.20	0.0242
Arteriolosclerosis			0.71	OR	
0 (none)	9 (23.7)	14 (31.1)		ref	
1 (mild)	12 (31.6)	13 (28.9)		1.91 (0.53–6.89)	0.32
2 (moderate)	12 (31.6)	15 (33.3)		1.40 (0.37–5.25)	0.62
3 (severe)	5 (13.2)	3 (6.7)		2.05 (0.27–15.7)	0.49
Braak score			0.12	OR	
1 or 2 (transentorhinal region)	4	1		ref	
3 or 4 (limbic regions)	25	27		0.36 (0.03–4.43)	0.42
5 (extensive neocortical regions)	7	15		0.18 (0.01–2.56)	0.21
Square root of average of NFT counts	0.65 ± 0.37	0.87 ± 0.36	0.0090	−0.35 ± 0.12	0.0070
Square root of tangle count in hippocampus CA1	3.9 ± 2.5	5.8 ± 2.8	0.0018	−2.35 ± 0.90	0.0169
Square root of tangle count in the entorhinal cortex	4.6 ± 2.3	5.6 ± 2.1	0.0318	−2.29 ± 0.77	0.0063
Square root of average of tangles in angular gyrus, inferior temporal, mid-frontal cortex, and superior frontal	0.86 ± 0.94	1.56 ± 1.45	0.0103	−1.0 ± 0.50	0.06
CERAD neuropathologic diagnosis of AD			0.75	OR	
1 (Definite)	12 (33.3)	19 (44.2)		0.66 (0.18–2.43)	0.53
2 (Probable)	12 (33.3)	12 (27.9)		0.91 (0.24–3.53)	0.90
3 (Possible)	2 (5.6)	3 (7.0)		0.29 (0.03–3.12)	0.31
4 (No AD)	10 (27.8)	9 (20.9)		ref	
Lewy body disease	7 (19.4)	5 (11.6)	0.34	2.29 (0.60–8.80)	0.23
Chronic Cerebral Infarctions	20 (55.6%)	23 (53.5%)	0.85	0.95 (0.34–2.67)	0.88
Gross Chronic Cerebral Infarctions	18 (50.0%)	21 (48.8%)	0.92	1.12 (0.41–3.10)	0.49
Micro Chronic Cerebral Infarctions	14 (38.9%)	11 (25.6%)	0.21	1.13 (0.33–3.82)	0.44

Amyloid level is the mean of square root transformation of amyloid score in 8 brain regions. Diffuse plaque is the average of 5 regions of scaled diffuse plaques. *Adjusted for baseline age, sex, race, education, systolic blood pressure, diabetes and depression. **HR (95% CI) for conversion to AD/dementia, OR for categorical outcomes, and % of difference or difference of least square means for continuous outcomes.

follow-up time and time between follow-up and death between both medication groups (Supplementary Table 2).

Conversion rates to AD stratified by antihypertensive medication use

We first needed to confirm there were differences in conversion rate from MCI to AD, for RAS-AHM acting versus non RAS-AHM users in the present study. As a whole, 14 of the 83 participants taking an AHM converted to AD, which is consistent with reported conversion rates of 10%–30% annually [25]. Conversion rate for RAS-AHM users was three (7.9%) and non RAS-AHM users was 11 (24.4%, $p = 0.02$). After adjusting for age, sex, race, education, systolic BP, diabetes, and depressive symptoms, the association between use of RAS-AHM use and conversion to AD remains significant (HR: 0.12, 95% CI: 0.02 – 0.80,

$p = 0.0285$). We found no violation of the proportional hazards assumption.

Neuropathological outcome stratified by antihypertensive medication use

Absolute numbers of plaques in hippocampus CA1 and entorhinal cortex were significantly lower in non RAS-AHM group (Supplementary Table 1). In the fully adjusted model, RAS users had significantly fewer overall NFTs ($p < 0.01$) and fewer tangles in all prespecified regions of interest including the hippocampal CA1 region ($p < 0.01$), the entorhinal cortex ($p < 0.01$), and the average number of NFT in brain regions including the angular gyrus, inferior temporal, mid-frontal cortex, and superior frontal ($p = 0.06$). RAS users also had higher brain weight ($p = 0.03$) and fewer diffuse plaques ($p = 0.02$). RAS-AHM and non RAS-AHM users did not differ on

neuropathological indices of NIA Reagan, amyloid burden, arteriolosclerosis, Lewy body disease, chronic, micro, or gross infarcts, Braak, or CERAD scores.

DISCUSSION

In our study we have shown that significantly fewer participants converted from MCI to AD when reporting the use of RAS-AHM for an average of four years. Additionally, we have also shown that RAS-AHM users exhibited fewer NFTs compared to individuals taking non RAS-AHM. These changes were present even after controlling for demographics and BP.

It is possible that the mechanism driving the AD–RAS relationship is primarily driven by tau versus amyloid, though RAS-AHM users had fewer diffuse plaques than non RAS-AHM users. It is also possible that because our participants had a diagnosis of MCI at baseline, amyloid levels had already stabilized, and thus an amyloid-RAS relationship may have been evident prior to MCI.

Research shows that blood-brain barrier crossing antihypertensives that act via the RAS may have the potential to reduce AD risk [26–28]. For instance, studies have shown that treatment with RAS-AHM attenuate age-related decreases in cerebrospinal fluid (CSF) Aβ [28], decrease AD incidence [29], and improve cognition in AD patients more so than non RAS-AHM [30]. Recently, RAS dysfunction in the brain has been implicated in AD via abnormal hyperphosphorylation of tau [31]. RAS-AHM are reportedly associated with lower levels of tau in CSF among individuals with MCI [14] and older individuals with normal cognition [28]. Notably, these benefits are observed irrespective of change in BP. The tau–RAS link may be particularly relevant during midlife and during prodromal disease stages [32].

There are few neuropathological studies exploring the role of RAS in AD. In the RAS, the primary function of ACE is the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. One study has shown increased ACE activity in the hippocampus, parahippocampal gyrus, frontal cortex, and caudate nucleus in AD patients [33]. Increased ACE levels have also been reported in postmortem AD brain tissue, in direct relation to parenchymal Aβ load [34] and Braak-staged AD severity [35].

Results are in line with our prior study reporting less disease progression among MCI patients taking

RAS-AHM versus non RAS-AHM [12]. In studies investigating conversion rate from MCI to AD, one study reported that treatment with any antihypertensive therapy was associated with slower disease conversion in participants with circulatory dysregulation. Other studies have reported protection from cognitive and functional decline in MCI patients, which was specific to RAS-acting medications, though neuropathological data were not available in these studies [36, 37]. Randomized clinical trials, however, including ONTARGET, TRANSCEND [38], PRoFESS [39], and PROGRESS [40] evaluating the effect of RAS-AHM on cognitive function as a secondary outcome, have shown no beneficial effect. Randomized controlled trials using RAS-AHM as an intervention against primary outcomes of cognitive decline and impairment are currently underway; however, results have yet to be reported [41].

Our results of an association between RAS-AHM use and tau are supported by work in both animal and human studies. A study in mice showed that Ang-(1–7), the main effector of the ACE2/Ang-(1–7)/Mas axis in the brain RAS, was implicated in the etiology and progression of AD via modulation of tau hyperphosphorylation [31]. The authors went on to report that findings have since been confirmed in a mouse model of pure tauopathy [42]. In another study, angiotensin II administered to mice induced significant cognitive impairment and significant tau phosphorylation via GSK3β activation. GSK3β activity was then attenuated by losartan, a RAS acting antihypertensive. One study in humans reported a link between CSF tau markers and RAS acting medications [14], showing that use of a RAS acting antihypertensives in individuals with MCI was associated with declines in tau and p-tau, over three years.

Our study had numerous strengths. Most cohort studies include cognitively normal individuals or those with established AD. In this study, we included only individuals with MCI at baseline since by identifying possible new treatment options in order to delay MCI conversion the number of new AD cases could be significantly reduced [22]. Our data show that clinically significant and measurable effects of RAS medication use are detectible during this prodromal disease phase, which is an optimal time to stage an intervention. Another major strength was that participants in all three cohorts were diagnosed with MCI at baseline using well validated diagnostic criteria. Another strength is the systematic collection

of neuropathological data which was identical across the three cohorts.

As with many observational studies, ours has also weaknesses. While having both clinical and neuropathological data for participants is a strength of the study, the sample size is still small, so results need to be interpreted with caution and replicated in a larger sample. Additionally, 33 of the of the 38 RAS-AHM users also reported concomitant use of non RAS-AHM during follow-up, limiting our conclusion. At the same time, it makes our findings even more striking, since multipole medication users may have more severe hypertension. Another limitation is that information regarding antihypertensive dose and length of administration was not available and should be considered in future studies. As is true in all observational studies, our results may also be vulnerable to confounding. In our study we have found that significantly higher number of men reported RAS-AHM use, raising the possibility of our results being partially explained by lower dementia risk associated with male sex [43]; however, adjustment for sex did not change our results. There may have been confounding by indication, because ACE-Is and A2RBs are the first line medications for treatment of congestive heart failure and for the prevention of renal insufficiency in people with diabetes mellitus; both are associated with dementia risk [44] and in our sample, participants on RAS-AHM had significantly higher prevalence of diabetes mellitus reflecting guidelines. Thus, our results are particularly noteworthy because RAS-AHM users had higher vascular disease burden, which is associated with increased dementia risk, and as such we would have expected higher conversion rate.

While the study included a preclinical AD sample, the mean age at baseline was over 80 years, which is likely decades after the AD-related brain changes began. More research in younger, high risk cohorts is needed to further promote brain changes from beginning (ex: AD parental history). Our study consists of research volunteers with more education and likely better overall cardiovascular health profiles than the general population and thus results may not be generalizable. However, we have no reason to believe that the effect of RAS medications differs between those with more or less education.

While the Rush cohorts include a large proportion of African Americans, the study is underrepresented with respect to postmortem neuropathological data in African American participants (seven African Americans versus seventy-six Caucasians). Because complete neuropathological data availability was an inclusion criterion of this study, we did not have adequate power to examine potential RAS induced neuropathological differences by race. Future studies should attempt to combine neuropathological data with clinical data obtained earlier in life than was able to be investigated in the present study. While our results suggest that RAS-AHM may slow disease progression, RAS-AHM may also play a role in the progression from normal cognitive aging to MCI.

In summary, results provide preliminary evidence that preservation of the RAS by means of using RAS-AHM may lessen the likelihood of developing AD, in individuals with MCI. Importantly, medications that act on the RAS are readily available and affordable, and it has been reported that use of RAS medications are able to significantly reduce ACE levels in the brain of middle aged, healthy individuals at risk for AD [27]. Further research, particularly clinical trials, investigating the influence of RAS-AHM on AD biomarkers during prodromal disease stages is warranted. Because CSF Aβ and tau levels are being established across the preclinical and clinical AD stages, studies utilizing collection of CSF will be particularly crucial to fully understanding the AD-RAS relationship to preclinical AD-related neuropathology. Targeting populations such as women and African Americans, who are at increased risk for AD, should also be of special interest. Phase IV clinical trials in both hypertensive and normotensive individuals at high risk for AD due to race, family history, or early cognitive dysfunction should be conducted to test whether a RAS modifying medication could be repurposed for AD indications in high risk populations.

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-190011.

REFERENCES

[1] Jorm AF, Jolley D (1998) The incidence of dementia: A meta-analysis. *Neurology* **51**, 728-733.

[2] Kehoe PG, Miners S, Love S (2009) Angiotensins in Alzheimer's disease - friend or foe? *Trends Neurosci* **32**, 619-628.

[3] Wright JW, Harding JW (2010) The brain RAS and Alzheimer's disease. *Exp Neurol* **223**, 326-333.

[4] Hajjar I, Rodgers K (2013) Do angiotensin receptor blockers prevent Alzheimer's disease? *Curr Opin Cardiol* **28**, 417-425.

[5] Ashby EL, Kehoe PG (2013) Current status of renin-angiotensin system-targeting anti-hypertensive drugs as therapeutic options for Alzheimer's disease. *Expert Opin Investig Drugs* **22**, 1229-1242.

[6] Kehoe GP, Wong S, Mulhim NAL, Palmer LE, Miners SJ (2016) Angiotensin-converting enzyme 2 is reduced in Alzheimer's disease in association with increasing amyloid-β and tau pathology. *Alzheimers Res Ther* **8**, 50.

[7] von Bohlen und Halbach O, Albrecht D (2006) The CNS renin-angiotensin system. *Cell Tissue Res* **326**, 599-616.

[8] Inaba S, Iwai M, Furuno M, Tomono Y, Kanno H, Senba I, Okayama H, Mogi M, Higaki J, Horiuchi M (2009) Continuous activation of renin-angiotensin system impairs cognitive function in renin/angiotensinogen transgenic mice. *Am J Hypertens* **53**, 356-362.

[9] Kehoe PG, Hibbs E, Palmer LE, Miners JS (2017) Angiotensin-III is increased in Alzheimer's disease in association with amyloid-β and tau pathology. *J Alzheimers Dis* **58**, 203-214.

[10] Yasar S, Xia J, Yao W, Furberg CD, Xue QL, Mercado CI, Fitzpatrick AL, Fried LP, Kawas CH, Sink KM, Williamson JD, DeKosky ST, Carlson MC (2013) Antihypertensive drugs increase risk of Alzheimer's disease: Ginkgo Evaluation of Memory Study. *Neurology* **81**, 896-903.

[11] Yasar S, Schuchman M, Peters J, Anstey KJ, Carlson MC, Peters R (2016) Relationship between antihypertensive medications and cognitive impairment: Part I. Review of Human studies and clinical trials. *Curr Hypertens Rep* **18**, 67.

[12] Wharton W, Goldstein FC, Zhao L, Steenland K, Levey AI, Hajjar I (2015) Modulation of renin-angiotensin system may slow conversion from mild cognitive impairment to Alzheimer's disease. *J Am Geriatr Soc* **63**, 1749-1756.

[13] Hajjar I, Brown L, Mack WJ, Chui H (2012) Impact of angiotensin receptor blockers on Alzheimer's disease neuropathology in a large brain autopsy study. *Arch Neurol* **69**, 1632-1638.

[14] Hajjar I, Levey A (2015) Association between angiotensin receptor blockers and longitudinal decline in tau in mild cognitive impairment. J*AMA Neurol* **2**, 1069-1070.

[15] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH (2011) Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 280-292.

[16] Craft S (2009) The role of metabolic disorders in Alzheimer disease and vascular dementia: Two roads converged. *Arch Neurol* **66**, 300-305.

[17] Saavedra JM (2012) Angiotensin II AT(1) receptor blockers as treatments for inflammatory brain disorders. *Clin Sci (Lond)* **123**, 567-590.

[18] Bennett DA, Schneider JA, Buchman AS, Barnes LL, Boyle PA, Wilson RS (2012) Overview and findings from the rush Memory and Aging Project. *Curr Alzheimer Res* **9**, 646-663.

[19] Bennett DA, Schneider JA, Arvanitakis Z, Wilson RS (2012) Overview and findings from the Religious Orders study. *Curr Alzheimer Res* **9**, 628-645.

[20] Bennett DA, Schneider JA, Buchman AS, Barnes LL, Boyle PA, Wilson RS (2012) Overview and findings from the Rush Memory and Aging Project. *Curr Alzheimer Res* **9**, 646–663.

[21] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 270-279.

[22] Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease (2007) *Alzheimers Dement* **3**, 186-191.

[23] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944.

[24] Schneider JA, Wilson RS, Cochran EJ, Bienias JL, Arnold SE, Evans DA, Bennett DA (2003) Relation of cerebral infarctions to dementia and cognitive function in older persons. *Neurology* **60**, 1082-1088.

[25] Devanand DP, Folz M, Gorlyn M, Moeller JR, Stern Y (1997) Questionable dementia: Clinical course and predictors of outcome. *J Am Geriatr Soc* **45**, 321-328.

[26] Sink KM, Leng X, Williamson J, Kritchevsky SB, Yaffe K, Kuller L, Yasar S, Atkinson H, Robbins M, Psaty B, Goff DC Jr (2009) Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: Results from the cardiovascular health study. *Arch Intern Med* **169**, 1195-1202.

[27] Wharton W, Stein JH, Korcarz C, Sachs J, Olson SR, Zetterberg H, Dowling M, Ye S, Gleason CE, Underbakke G, Jacobson LE, Johnson SC, Sager MA, Asthana S, Carlsson CM (2012) The effects of ramipril in individuals at risk for Alzheimer's disease: Results of a pilot clinical trial. *J Alzheimers Dis* **32**, 147-156.

[28] Nation DA, Ho J, Yew B, Alzheimer's Disease Neuroimaging Initiative (2015) Older adults taking AT1-receptor blockers exhibit reduced cerebral amyloid retention. *J Alzheimers Dis* **50**, 779-789.

[29] Ohrui T, Matsui T, Yamaya M, Arai H, Ebihara S, Maruyama M, Sasaki H (2004) Angiotensin-converting enzyme inhibitors and incidence of Alzheimer's disease in Japan. *J Am Geriatr Soc* **52**, 649-650.

[30] Ohrui T, Tomita N, Sato-Nakagawa T, Matsui T, Maruyama M, Niwa K, Arai H, Sasaki H (2004) Effects of

brain-penetrating ACE inhibitors on Alzheimer disease progression. *Neurology* **63**, 1324-1325.

[31]   Jiang T, Zhang YD, Zhou JS, Zhu XC, Tian YY, Zhao HD, Lu H, Gao Q, Tan L, Yu JT (2016) Angiotensin-(1-7) is reduced and inversely correlates with tau hyperphosphorylation in animal models of Alzheimer's disease. *Mol Neurobiol* **53**, 2489-2497.

[32]   Ho JK, Nation DA, Alzheimer's Disease Neuroimaging Initiative (2017) Memory is preserved in older adults taking AT1 receptor blockers. *Alzheimers Res Ther* **9**, 33.

[33]   Savaskan E, Hock C, Olivieri G, Bruttel S, Rosenberg C, Hulette C, Muller-Spahn F (2001) Cortical alterations of angiotensin converting enzyme, angiotensin II and AT1 receptor in Alzheimer's dementia. *Neurobiol Aging* **22**, 541-546.

[34]   Miners JS, Ashby E, Van Helmond Z, Chalmers KA, Palmer LE, Love S, Kehoe PG (2008) Angiotensin-converting enzyme (ACE) levels and activity in Alzheimer's disease, and relationship of perivascular ACE-1 to cerebral amyloid angiopathy. *Neuropathol Appl Neurobiol* **34**, 181-193.

[35]   Miners JS, van Helmond Z, Raiker M, Love S, Kehoe PG (2010) ACE variants and association with brain Abeta levels in Alzheimer's disease. *Am J Transl Res* **3**, 73-80.

[36]   Rozzini L, Chilovi BV, Bertoletti E, Conti M, Del Rio I, Trabucchi M, Padovani A (2006) Angiotensin converting enzyme (ACE) inhibitors modulate the rate of progression of amnestic mild cognitive impairment. *Int J Geriatr Psychiatry* **21**, 550-555.

[37]   Hajjar I, Hart M, Chen YL, Mack W, Novak V, H CC, Lipsitz L (2013) Antihypertensive therapy and cerebral hemodynamics in executive mild cognitive impairment: Results of a pilot randomized clinical trial. *J Am Geriatr Soc* **61**, 194-201.

[38]   The PROGRESS Collaborator Group (2003) Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients wityh cerebrovascular disease. *Arch Intern Med* **163**, 1069-1075.

[39]   Diener HC, Sacco RL, Yusuf S (2008) Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: A double-blind, active and placebo -controlled study. *Lancet Neurol* **10**, 875-884.

[40]   Anderson C, Teo K, Gao P, Arima H, Dans A, Unger T, Commerford P, Dyal L, Schumacher H, Pagua J, Paolasso E, Holwerda N, Chazova I, Binbrek A, Young J, Yusuf S, for the ONTARGET and TRASCEND Investigators (2011) Renin-angiotensin systemt blockade and cognitive function in patients at high risk of cardiovascular disease: Analysis of data from the ONTARGET and TRANSCEND studies. *Lancet Neurol* **10**, 43-53.

[41]   Kehoe PG (2018) The coming of age of angiotensin hypothesis in Alzheimer's disease: Progress toward disease prevention and treatment? *J Alzheimer Dis* **62**, 443-466.

[42]   Ozcelik S, Fraser G, Castets P, Schaeffer V, Skachokova Z, Breu K, Clavaguera F, Sinnreich M, Kappos L, Goedert M, Tolnay M, Winkler DT (2013) Rapamycin attenuates the progression of tau pathology in P301S tau transgenic mice. *PLoS One* **8**, e62459.

[43]   Mielke MM (2018) Sex and gender differences in Alzheimer's disease dementia. *Psychiatr Times* **35**, 14-17.

[44]   Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, McGovern P, Folsom AR, Atherosclerosis Risk in Communities (ARIC) Study Investigators (2001) Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology* **56**, 42-48.