Title
Antihypertensive drugs decrease risk of Alzheimer disease

Journal
Neurology, 81(10)

ISSN
0028-3878

Authors
Yasar, Sevil
Xia, Jin
Yao, Wenliang
et al.

Publication Date
2013-09-03

DOI
10.1212/wnl.0b013e3182a35228

Antihypertensive drugs decrease risk of Alzheimer disease

Ginkgo Evaluation of Memory Study

Sevil Yasar, MD, PhD
Jin Xia, MS
Wenliang Yao, PhD
Curt D. Furberg, MD, PhD
Qian-Li Xue, PhD
Carla I. Mercado, PhD
Annette L. Fitzpatrick, PhD
Linda P. Fried, MD
Claudia H. Kawas, MD
Kaycee M. Sink, MD
Jeff D. Williamson, MD
Steven T. DeKosky, MD
Michelle C. Carlson, PhD
For the Ginkgo Evaluation of Memory (GEM) Study Investigators

Correspondence to Dr. Yasar: syasar1@jhmi.edu

ABSTRACT

Objectives: The aim of this study was to determine whether use of diuretics, angiotensin-1 receptor blockers (ARB), angiotensin-converting enzyme inhibitors (ACE-I), calcium channel blockers (CCB), or β-blockers (BB) was associated with a reduced risk of Alzheimer disease (AD) dementia in participants with normal cognition or mild cognitive impairment (MCI).

Methods: Secondary longitudinal data analysis of the Ginkgo Evaluation of Memory Study in older adults at least 75 years of age with normal cognition (n = 1,928) or MCI (n = 320) over a median 6.1-year period using Cox proportional hazard models after adjusting for confounders.

Results: Diuretic use was reported by 15.6%, ARB 6.1%, ACE-I 15.1%, CCB 14.8%, and BB 20.5%. Of the 2,248 participants, 290 (13%) developed AD dementia. Hazard ratio for incident AD dementia among participants with normal cognition was 0.51 in diuretic (95% confidence interval [CI] 0.31–0.82), 0.31 in ARB (95% CI 0.14–0.68), 0.50 in ACE-I (95% CI 0.29–0.83), 0.62 in CCB (95% CI 0.35–1.09), and 0.58 in BB (95% CI 0.36–0.93) users and was not significantly altered when mean systolic blood pressure was above 140 mm Hg. In participants with MCI, only diuretic use was associated with decreased risk (hazard ratio = 0.38, 95% CI 0.20–0.73).

Conclusions: Diuretic, ARB, and ACE-I use was, in addition to and/or independently of mean systolic blood pressure, associated with reduced risk of AD dementia in participants with normal cognition, while only diuretic use was associated with reduced risk in participants with MCI.

Neurology® 2013;81:896–903

GLOSSARY

ACE-I = angiotensin-converting enzyme inhibitor; **AD** = Alzheimer disease; **ARB** = angiotensin-1 receptor blocker; **BB** = β-blocker; **CCB** = calcium channel blocker; **CHF** = congestive heart failure; **CI** = confidence interval; **DBP** = diastolic blood pressure; **DM** = diabetes mellitus; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **GEMS** = Ginkgo Evaluation of Memory Study; **HR** = hazard ratio; **HTN** = hypertension; **MCI** = mild cognitive impairment; **RAS** = renin-angiotensin system; **SBP** = systolic blood pressure.

Observational studies suggest protective effects of antihypertensive medications on risk of dementia[1–6] independently or in addition to their ability to control blood pressure, and that these effects may be specific to the class of drugs to which they belong. A postmortem study of subjects with Alzheimer disease (AD) dementia showed that treated hypertensive subjects had less AD dementia neuropathology than untreated hypertensive and normotensive subjects,[7] while imaging studies showed preserved hippocampus in normotensive and treated hypertensive subjects.[8,9] However, clinical trials evaluating antihypertensive medications for dementia prevention found no risk reduction,[10–12] which could be explained by dementia being a secondary outcome and therefore insufficiently powered. Additionally, the majority of these studies were confounded by combined antihypertensive medication use[11,13–16] to achieve acceptable blood pressure. There are few studies with equivocal evidence regarding the role of hypertension (HTN) and no randomized clinical trials evaluating the effects of antihypertensive medications on progression of mild cognitive impairment (MCI) to dementia.[17–19]

Editorial, page 860

See page 888

Supplemental data at www.neurology.org

From The Johns Hopkins University (S.Y., J.X., W.Y., Q.-L.X., L.P.F., M.C.C.), Baltimore, MD; Wake Forest School of Medicine (C.D.F., K.M.S., J.D.W.), Winston-Salem, NC; University of Washington (C.I.M., A.L.F.), Seattle; Columbia University (L.P.F.), New York; University of California (C.H.K., S.T.D.), Irvine; University of Pittsburgh (C.H.K., S.T.D.), PA; and University of Virginia (S.T.D.), Charlottesville.

The GEM Study Investigators are listed on the *Neurology*® Web site at www.neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

We hypothesized that antihypertensive medications, especially diuretics, angiotensin-1 receptor blockers (ARB), and calcium channel blockers (CCB), would decrease the risk of AD dementia in people with mild or no cognitive impairment. In this larger national study, the Ginkgo Evaluation of Memory Study (GEMS),[20] which showed no benefit of ginkgo biloba in reducing incidence of dementia,[21] we examined whether reported diuretic, ARB, angiotensin-converting enzyme inhibitor (ACE-I), CCB, or β-blocker (BB) use was associated with decreased risk of developing AD dementia in participants with mild or no cognitive impairment.

METHODS

Participants and study design. This study is a post hoc analysis of the randomized controlled GEMS trial. GEMS was a double-blind, randomized, controlled clinical trial of 3,069 individuals without dementia, aged between 75 and 96 years recruited from 4 US communities: Hagerstown, MD; Pittsburgh, PA; Winston-Salem/Greensboro, NC; and Sacramento, CA to assess ginkgo biloba 240 mg/d vs placebo for the prevention of dementia over a median period of 6.1 years. Details and results of the study have been published.[20–22] At each stage of the recruitment process, cognitive, medical, and other exclusion criteria were applied.[21]

Screening visits included the modified Mini-Mental State Examination,[23] and participants with a score of 80 or more progressed to a more rigorous battery of 14 neuropsychological tests.[20] Participants were eligible for entry into GEMS if they achieved passing scores in at least 6 of the 7 cognitive domains and met all other criteria for normal cognitive function or MCI.[20]

Demographic and baseline health characteristics were assessed using questionnaires including age, race, sex, and years of education. Medical history was based on self-report of a history of 16

Table 1 Baseline characteristics of study participants[a]

		Participants included in analysis (n = 2,248)					
	All participants (n = 3,069)	No antihypertensive medication (n = 643)	ARB (n = 140)	Diuretic (n = 351)	ACE-I (n = 324)	CCB (n = 333)	BB (n = 457)
Sex, n (%)							
Female	1,418 (46.2)	312 (48.5)	72 (51.4)	188 (53.6)	125 (38.6)[b]	157 (47.1)	187 (40.9)
Income/y, n (%)							
<$36,000	801 (26.1)	158 (24.6)	39 (27.8)	91 (25.9)	89 (27.5)	82 (24.6)	131 (28.7)
$36,000–$52,000	1,434 (46.7)	291 (45.3)	64 (45.7)	183 (52.1)[c]	133 (41.0)	158 (47.4)	202 (44.2)
>$52,000	820 (26.2)	193 (30.1)	37 (26.5)	75 (21.4)[c]	97 (29.0)	92 (27.6)	124 (27.1)
Smoking, n (%)							
Former	1,651 (53.8)	325 (50.5)	75 (53.6)	179 (51.0)	182 (56.2)	198 (59.4)	233 (51.0)
Current	136 (4.4)	33 (5.1)	4 (2.9)	18 (5.1)	16 (4.9)	14 (4.2)	20 (4.4)
History, n (%)							
Hypertension	1,306 (42.6)	9 (1.4)	68 (48.6)[d]	155 (44.2)[d]	170 (52.5)[d]	184 (55.2)[d]	186 (40.7)[d]
Diabetes	277 (9.0)	28 (4.4)	9 (6.4)	20 (5.7)	51 (15.7)[d]	22 (6.6)	41 (9.0)[b]
Heart attack	300 (9.8)	24 (3.7)	9 (6.4)	25 (7.1)[c]	18 (5.6)	35 (10.5)[d]	65 (14.2)[d]
Angina	304 (9.9)	17 (2.6)	16 (11.4)[d]	22 (6.3)[b]	25 (7.7)[b]	37 (11.1)[d]	62 (13.6)[d]
Stroke	88 (2.9)	10 (1.6)	4 (2.9)	11 (3.1)	10 (3.1)	7 (2.1)	13 (2.8)
TIA	221 (7.2)	22 (3.4)	11 (7.9)[c]	21 (6.0)	23 (7.1)[b]	40 (12.0)[d]	33 (7.2)[b]
Heart failure	61 (2.0)	4 (0.6)	1 (0.7)	7 (2.0)	7 (2.2)	3 (0.1)	3 (0.6)
MCI	482 (15.7)	101 (15.7)	16 (11.4)	40 (11.4)	48 (14.8)	52 (15.6)	54 (11.8)
Age, mean (SD)	78.6 (3.3)	78.3 (3.1)	78.5 (3.3)	78.7 (3.5)	78.8 (3.2)	79.3 (3.8)[d]	78.4 (2.9)
Education, mean (SD)	14.3 (3.0)	14.6 (3.1)	13.9 (2.6)	14.2 (2.9)	14.3 (3.1)	14.1 (2.8)	14.4 (3.0)
Body mass index, mean (SD)	27.1 (4.3)	25.7 (3.9)	27.4 (4.0)[d]	28.0 (4.5)[d]	27.4 (4.1)[d]	26.7 (4.1)[d]	27.0 (4.1)[d]
Systolic blood pressure, mean (SD)	133.0 (18.3)	126.1 (15.5)	138.9 (17.5)[d]	131.3 (16.8)[d]	135.0 (18.3)[d]	137.8 (18.7)[d]	135.4 (18.8)[d]
Diastolic blood pressure, mean (SD)	68.9 (9.8)	67.89 (8.7)	71.3 (9.4)[d]	69.2 (9.5)	69.4 (10.5)[c]	69.6 (10.4)[b]	70.1 (10.2)[d]

Abbreviations: ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-1 receptor blocker; BB = β-blocker; CCB = calcium channel blocker; MCI = mild cognitive impairment.

[a] ARB, diuretics, ACE-I, CCB, and BB were each used without concurrent use of any other type of antihypertensive medication. Each antihypertensive medication user group was compared with the no antihypertensive medication user group.

[b] $p < 0.005$.

[c] $p < 0.01$

[d] $p < 0.001$.

diseases, including myocardial infarction, angina, stroke, TIA, heart failure, HTN, diabetes mellitus (DM), and atrial fibrillation.

Standard protocol approvals, registrations, and patient consents. This study was approved by an Institutional Review Board at each investigational center, and patients provided written informed consent before participation. This study was conducted in compliance with the Declaration of Helsinki and all International Conference on Harmonization Good Clinical Practice Guidelines, and is registered on Clinicaltrials.gov (NCT00010803).

Exposure assessment. Detailed information about medication use was collected at each visit by visually inspecting prescribed and over-the-counter medications. Medication names, doses, frequencies, and routes of administration taken in the prior 2 weeks were entered in a medication database designed to match each drug with a numerical code that could be used for categorizing drugs. Medications were coded by drug class as diuretics (amiloride, bumetanide, chlorthalidone, chlorothiazide, furosemide, hydrochlorothiazide, indapamide, metolazone, methylchlorothiazide, spironolactone, torsemide, triamterene), ARB (candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan), ACE-I (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril), CCB (amlodipine, bepridil, felodipine, diltiazem, isradipine, mibefradil, nicardipine, nifedipine, nisoldipine, verapamil), or BB (acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol, penbutolol, pindolol, propranolol).

Table 2 HRs from Cox regression analyses: AD associated with ARB, ACE-I, diuretic, BB, and CCB medication use in participants with normal cognition and MCI at baseline[a]

	AD (n = 290)			
	Model 1 (unadjusted)		Model 2 (adjusted: age, sex, education, income, no. of vascular diseases, BMI, SBP, DBP, MCI)	
Medication[b]	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
ARB vs none	0.44 (0.26–0.75)	0.02[c]	0.35 (0.19–0.65)	0.001[d]
ARB vs ACE-I	0.66 (0.34–1.26)	0.21	0.63 (0.32–1.25)	0.18
ARB vs diuretic	0.76 (0.42–1.40)	0.38	0.75 (0.39–1.42)	0.37
ARB vs BB	0.59 (0.32–1.10)	0.10	0.55 (0.29–1.05)	0.07
ARB vs CCB	0.55 (0.30–0.99)	0.05	0.63 (0.33–1.19)	0.16
ACE-I vs none	0.62 (0.44–0.87)	0.005[c]	0.56 (0.37–0.85)	0.001[d]
ACE-I vs diuretic	1.03 (0.70–1.50)	0.86	1.05 (0.70–1.52)	0.80
ACE-I vs BB	0.90 (0.61–1.33)	0.60	0.79 (0.53–1.18)	0.24
ACE-I vs CCB	0.79 (0.53–1.20)	0.27	0.94 (0.62–1.44)	0.79
Diuretic vs none	0.59 (0.43–0.82)	0.002[c]	0.46 (0.32–0.68)	<0.001[d]
Diuretic vs BB	0.89 (0.61–1.03)	0.55	0.68 (0.54–1.18)	0.26
Diuretic vs CCB	0.76 (0.51–1.13)	0.17	0.78 (0.51–1.17)	0.23
BB vs none	0.66 (0.48–0.91)	0.01[e]	0.64 (0.44–0.72)	0.01[e]
BB vs CCB	0.90 (0.60–1.35)	0.61	1.11 (0.72–1.69)	0.90
CCB vs none	0.78 (0.55–1.10)	0.17	0.67 (0.93–1.04)	0.07

Abbreviations: ACE-I = angiotensin-converting enzyme inhibitor; AD = Alzheimer disease; ARB = angiotensin-1 receptor blocker; BB = β-blocker; BMI = body mass index; CCB = calcium channel blocker; CI = confidence interval; DBP = diastolic blood pressure; HR = hazard ratio; MCI = mild cognitive impairment; SBP = systolic blood pressure.
[a] ARB, diuretics, ACE-I, CCB, and BB were each used without concurrent use of any other type of antihypertensive medication.
[b] None = no antihypertensive medication use.
[c] $p < 0.005$.
[d] $p < 0.001$.
[e] $p < 0.01$.

Outcome measures. The primary outcome of this post hoc analysis was incidence of AD dementia among different antihypertensive medication user groups. AD dementia was diagnosed by a multidisciplinary panel of experts, who were blinded to treatment group assignments, using criteria of *DSM-IV*[24] and the National Institute of Neurological and Communication Disorders and Stroke–Alzheimer's Disease and Related Disorders Association,[25] as previously described in more detail.[20,21]

Statistical analyses. Because in the initial trial ginkgo biloba was not effective in reducing AD dementia incidence,[21] all participants were included in our study. Of 3,069 participants without dementia at baseline, we excluded 821 from analysis who had no follow-up visit or reported concomitant use of any of the antihypertensive medication groups at baseline or during follow-up. Of the 2,248 included in the final analysis, 351 reported diuretic, 140 ARB, 324 ACE-I, 333 CCB, and 457 BB use. To maintain adequate sample size and statistical power, similar to a previous study,[6] we allowed a switch to another antihypertensive medication group during follow-up visits. We also examined associations on risk of AD dementia using a model that allowed use of only one antihypertensive medication group throughout the whole study and found similar, but less significant, effects, possibly because of inadequate power.

We compared baseline characteristics between diuretic, ARB, ACE-I, CCB, and BB with no antihypertensive medication users by using χ^2 tests for categorical and Wilcoxon rank sum test for continuous variables. Continuous-time Cox proportional hazard regression models were used to assess hazard ratios (HRs) of AD dementia associated with diuretic, ARB, ACE-I, CCB, or BB use by using SAS version 9.1 (SAS Institute Inc., Cary, NC). Because of the numerous comparisons, the a priori *p* value was set at <0.01.

First, we evaluated associations between diuretic, ARB, ACE-I, CCB, BB, and no antihypertensive medication use and risk of AD dementia in participants with normal cognitive function and MCI at baseline, comparing each group with the others. Then, in separate analyses, we evaluated the same associations in participants with normal cognition or MCI at baseline. Finally, we stratified subjects according to their mean systolic blood pressure (SBP) during the entire study as either above or below 140 mm Hg, to evaluate the possible role of HTN among antihypertensive medication user groups and the risk of AD dementia.

Analyses in model 1 were unadjusted and in model 2 adjusted for potential confounding effects of age, sex, years of education, income (<$36,000/y, $36,000–$52,000/y, >$52,000/y), smoking history, body mass index (kg/m^2), SBP, diastolic blood pressure (DBP), MCI status at baseline, and number of vascular diseases at baseline. The variable of "number of vascular diseases" was used to reduce the number of confounders, after we separately assessed individual vascular diseases, and found no significant associations between risk of AD dementia and diseases such as history of HTN, stroke, myocardial infarction or angina, congestive heart failure (CHF), peripheral artery disease, and DM.

The associations between duration of medication use and risk of AD dementia were analyzed as an ordinal duration-of-use variable (reported no use, use in one examination only, or use in 2 or more nonconsecutive examinations), which allowed us to measure risk of AD dementia in relation to duration of medication use.

Because HTN, the indication of antihypertensive medication use, and AD dementia both are associated with increased risk of mortality, we also performed competing risk regression analysis between incidence of AD dementia and incidence of death among the different antihypertensive medication user groups

and non-antihypertensive medication users, and found that incidence of mortality was not higher than incidence of AD dementia, suggesting no competing risk of mortality.

RESULTS Average age of the 2,248 participants was 78.7 years, 47% were female, mean education was 14.2 years, and they were followed over a median 6.1-year period.

Of the antihypertensive medication users, 50% reported HTN, and mean SBP (SD) and DBP (SD) on treatment at baseline were 130.9 (17.6) and 69.6 (9.8) mm Hg, while of the no antihypertensive medication user group, 1.4% reported HTN, and mean SBP (SD) and DBP (SD) at baseline were 126.1 (15.5) and 67.9 (8.7) mm Hg. Antihypertensive medication use was reported by 71.4%, with 6.2% reporting ARB, 15.6% reporting diuretic, 14.4% reporting ACE-I, 14.8% reporting CCB, and 20.3% reporting BB (table 1).

When comparing the different antihypertensive medication user groups to no antihypertensive medication users, the prevalence of HTN among ARB (49%), diuretic (44%), ACE-I (52%), CCB (55%), and BB (41%) users was significantly higher, but there was no difference among different antihypertensive medication groups. Similarly, prevalence of myocardial infarction and angina was higher among diuretic, ACE-I, CCB, and BB users but similar among the different medication user groups. The prevalence of CHF and DM was similar across all medication user groups and the non-antihypertensive medication user group, with the exception of ACE-I users. The prevalence of strokes between antihypertensive medication user groups and nonusers was similar. Mean age was slightly higher in the CCB user group. Body mass index was higher in all antihypertensive medication user groups, but was similar when compared with each other. The mean SBP and DBP were higher among ARB, CCB, and BB users compared with nonusers; however, they were similar among all antihypertensive medication user groups (table 1). Over an average of 5.6 years, of the 1,928 with normal cognition at baseline, 180 developed AD dementia, and of the 320 with MCI at baseline, 110 developed AD dementia.

In participants with normal cognition and MCI at baseline, use of diuretic (HR = 0.46, 95% CI 0.32–0.68; $p < 0.001$), ARB (HR = 0.35, 95% CI 0.19–0.65; $p = 0.001$), ACE-I (HR = 0.56, 95% CI 0.37–0.85; $p = 0.001$), and BB (HR = 0.64, 95% CI 0.44–0.72; $p = 0.01$) was associated with significant reductions in incident AD dementia compared with no antihypertensive medication users, while CCB use was not (HR = 0.67, 95% CI 0.93–1.04; $p = 0.07$) (table 2).

Similar reductions were seen in participants with normal cognition at baseline among users of diuretics (HR = 0.51, 95% CI 0.31–0.82; $p = 0.006$), ARB (HR = 0.31, 95% CI 0.14–0.68; $p = 0.003$), and ACE-I (HR = 0.50, 95% CI 0.29–0.83; $p = 0.008$) (table 3) when compared with no antihypertensive medication users. In participants with MCI at baseline, only diuretic use was associated with a significant risk reduction (HR = 0.38, 95% CI 0.20–0.73; $p = 0.004$). However, there was a similar trend in participants using ARB, ACE-I, or BB (table 4), which suggests lack of power.

When medication use was reported in 2 or more examinations, risk of AD dementia among diuretic users was HR = 0.40 (95% CI 0.26–0.61; $p < 0.0001$) and among ARB users was HR = 0.37 (95% CI 0.19–0.72; $p = 0.004$) (table 5) compared with the no antihypertensive medication users.

We then stratified subjects in each medication user group according to their mean SBP throughout the whole study as either above or below 140 mm Hg, to evaluate the possible role of HTN among antihypertensive medication user groups and the risk of AD dementia. We found no difference in risk among diuretic (HR = 1.06, 95% CI 0.50–2.24; $p = 0.88$),

Table 3 HRs from Cox regression analyses: AD associated with ARB, ACE-I, diuretic, BB, and CCB medication use in participants with normal cognition at baseline[a]

	AD (n = 180)			
	Model 1 (unadjusted)		Model 2 (adjusted: age, sex, education, income, no. of vascular diseases, BMI, SBP, DBP)	
Medication[b]	HR (95% CI)	p Value	HR (95% CI)	p Value
ARB vs none	0.48 (0.24-0.95)	0.04	0.31 (0.14-0.68)	0.003[c]
ARB vs ACE-I	0.62 (0.27-1.40)	0.25	0.68 (0.29-1.55)	0.36
ARB vs diuretic	0.74 (0.36-1.53)	0.42	0.76 (0.36-1.59)	0.47
ARB vs BB	0.50 (0.27-1.12)	0.09	0.58 (0.26-1.32)	0.20
ARB vs CCB	0.47 (0.21-1.02)	0.06	0.64 (0.28-1.47)	0.29
ACE-I vs none	0.74 (0.48-1.14)	0.17	0.50 (0.29-0.83)	0.008[c]
ACE-I vs diuretic	0.99 (0.62-1.59)	0.97	1.02 (0.62-1.65)	0.95
ACE-I vs BB	0.90 (0.55-1.46)	0.66	0.87 (0.53-1.42)	0.58
ACE-I vs CCB	0.78 (0.47-1.30)	0.34	0.87 (0.51-1.47)	0.60
Diuretic vs none	0.74 (0.49-1.11)	0.15	0.51 (0.31-0.82)	0.006[c]
Diuretic vs BB	0.90 (0.57-1.42)	0.65	0.90 (0.56-1.45)	0.66
Diuretic vs CCB	0.81 (0.50-1.32)	0.40	0.89 (0.54-1.48)	0.65
BB vs none	0.77 (0.51-1.15)	0.20	0.58 (0.36-0.93)	0.02
BB vs CCB	0.93 (0.56-1.56)	0.80	1.07 (0.63-1.80)	0.80
CCB vs none	0.91 (0.58-1.42)	0.67	0.62 (0.35-1.09)	0.10

Abbreviations: ACE-I = angiotensin-converting enzyme inhibitor; AD = Alzheimer disease; ARB = angiotensin-1 receptor blocker; BB = β-blocker; BMI = body mass index; CCB = calcium channel blocker; CI = confidence interval; DBP = diastolic blood pressure; HR = hazard ratio; SBP = systolic blood pressure.

[a] ARB, diuretics, ACE-I, CCB, and BB were each used without concurrent use of any other type of antihypertensive medication.

[b] None = no antihypertensive medication use.

[c] $p \leq 0.005$.

Table 4 HRs from Cox regression analyses: AD associated with ARB, ACE-I, diuretic, BB, and CCB medication use in participants with MCI at baseline[a]

	AD (n = 110)			
	Model 1 (unadjusted)		Model 2 (adjusted: age, sex, education, income, no. of vascular diseases, BMI, SBP, DBP)	
Medication[b]	HR (95% CI)	p Value	HR (95% CI)	p Value
ARB vs none	0.36 (0.15–0.84)	0.02	0.37 (0.13–1.06)	0.06
ARB vs ACE-I	0.78 (0.26–2.33)	0.65	0.21 (0.04–0.99)	0.05
ARB vs diuretic	0.99 (0.32–3.03)	0.99	1.12 (0.29–4.30)	0.87
ARB vs BB	0.68 (0.26–1.84)	0.45	0.56 (0.18–1.75)	0.32
ARB vs CCB	0.78 (0.30–2.00)	0.61	0.40 (0.13–1.24)	0.11
ACE-I vs none	0.45 (0.26–0.79)	0.005[c]	0.53 (0.26–1.08)	0.08
ACE-I vs diuretic	1.09 (0.55–2.15)	0.81	1.13 (0.55–2.33)	0.74
ACE-I vs BB	0.61 (0.30–1.22)	0.16	0.82 (0.39–1.75)	0.61
ACE-I vs CCB	0.79 (0.39–1.60)	0.52	0.94 (0.43–2.01)	0.89
Diuretic vs none	0.39 (0.22–0.69)	0.001[d]	0.38 (0.20–0.73)	0.004[c]
Diuretic vs BB	0.64 (0.32–1.25)	0.19	0.58 (0.28–1.23)	0.16
Diuretic vs CCB	0.66 (0.32–1.34)	0.25	0.38 (0.17–0.86)	0.02
BB vs none	0.60 (0.35–1.02)	0.06	0.56 (0.30–1.01)	0.05
BB vs CCB	1.13 (0.57–2.26)	0.72	1.04 (0.47–2.27)	0.93
CCB vs none	0.56 (0.31–0.98)	0.04	0.79 (0.37–1.66)	0.53

Abbreviations: ACE-I = angiotensin-converting enzyme inhibitor; AD = Alzheimer disease; ARB = angiotensin-1 receptor blocker; BB = β-blocker; BMI = body mass index; CCB = calcium channel blocker; CI = confidence interval; DBP = diastolic blood pressure; HR = hazard ratio; MCI = mild cognitive impairment; SBP = systolic blood pressure.
[a] ARB, diuretics, ACE-I, CCB, and BB were each used without concurrent use of any other type of antihypertensive medication.
[b] None = no antihypertensive medication use.
[c] $p \leq 0.005$.
[d] $p \leq 0.001$.

ARB (HR = 2.85, 95% CI 0.87–9.28; $p = 0.08$), ACE-I (HR = 0.97, 95% CI 0.52–1.82; $p = 0.93$), CCB (HR = 0.62, 95% CI 0.30–1.30; $p = 0.20$), or no antihypertensive medication user groups (HR = 0.78, 95% CI 0.42–1.45; $p = 0.43$), with the exception of BB (HR = 2.00, 95% CI 1.10–3.61; $p = 0.02$).

DISCUSSION In this post hoc longitudinal analysis of the randomized controlled GEMS trial of community-dwelling older participants without dementia, we evaluated associations between different antihypertensive medication use (diuretics, ARB, ACE-I, CCB, and BB) on incidence of AD dementia. We demonstrated that diuretic use was associated with at least a 50% decreased risk of developing AD dementia and was not significantly altered when mean SBP was above 140 mm Hg, compared with never users. These associations were even stronger, with a risk reduction of 60%, when medication use was reported in 2 or more examinations, replicating previous results by the Rotterdam Study.[5] ARB and ACE-I use was also associated with a 40% to 50% decreased risk, but only among participants with normal cognition at baseline. Notably, similar trends for risk reduction were seen among participants with MCI at baseline. BB use was associated with a similar, but smaller effect. In contrast, CCB use, similar to previous observational studies,[1,26] was not associated with risk reduction.

It has been suggested that the renin-angiotensin system (RAS) has a role in AD dementia by a vascular pathway, in which angiotensin II, cleaved from angiotensin I by ACE, acts on angiotensin 1 receptors, resulting in vasoconstriction and subsequently in decreased blood flow; and by a neurodegenerative pathway, in which ACE is involved in increasing amyloid-β degradation, while angiotensin II inhibits acetylcholine release and has proinflammatory properties.[26,27] Thus, the associations seen between risk of AD dementia and ARB use, which blocks the effects of angiotensin II, and ACE-I use, which blocks the conversion of angiotensin I to angiotensin II, could be explained by their actions on the RAS.

The case for the protective effect of diuretics is not clear; however, it was suggested that diuretics, similar to ARB, also increase angiotensin II,[26] so their effects could be partially explained by effects on the RAS. We were not able to confirm previous study results[4] of decreased risk of AD dementia mainly among potassium-sparing diuretic users because we found similarly decreased risk of AD dementia among potassium-sparing and nonsparing diuretics (results not shown).

Despite the small number of ARB users in our study, we confirmed previous findings in a large population sample of 800,000 predominantly male participants with normal cognition at baseline, which showed that ARB use was associated with reduced risk of developing AD dementia.[6] We were unable to reproduce their findings of superiority of ARB over ACE-I in decreasing AD dementia risk, which could be attributable to either the smaller number of participants using ARB or a drug-specific effect, because their ACE-I group consisted only of lisinopril users, which according to a recent study showed that enalapril, but not lisinopril, was associated with decreased risk of developing MCI.[28]

Previous studies have shown associations between elevated blood pressure and incidence of AD dementia[1]; thus, blood pressure control should result in decreased incidence of AD dementia. However, studies have also suggested that antihypertensive medications may have protective effects in addition and or independently of blood pressure control and that the effects may be specific to the class of drugs to which they belong. We found that when mean SBP during the entire study was above 140 mm Hg, it did not significantly alter the risk of AD dementia among diuretic,

Table 5 HRs from Cox regression analyses: AD associated with length of medication use (ARB, ACE-I, diuretic, BB, and CCB) in participants with normal cognition and MCI at baseline[a]

	AD			
	Model 1 (unadjusted)		Model 2 (adjusted: age, sex, education, income, no. of vascular diseases, BMI, SBP, DBP, MCI)	
Medication	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Diuretic				
Never used				
1	0.98 (0.61–1.59)	0.94	0.71 (0.41–1.23)	0.22
≥2	0.49 (0.39–0.71)	0.0002[b]	0.40 (0.26–0.61)	<0.0001[b]
ACE-I				
Never used				
1	0.55 (0.43–0.97)	0.004[c]	0.47 (0.25–0.88)	0.01[d]
≥2	0.65 (0.45–0.95)	0.003[c]	0.60 (0.38–0.94)	0.02
ARB				
Never used				
1	0.39 (0.14–1.07)	0.07	0.29 (0.09–0.95)	0.04
≥2	0.46 (0.25–0.84)	0.01[d]	0.37 (0.19–0.72)	0.004[c]
CCB				
Never used				
1	0.81 (0.44–1.47)	0.48	0.67 (0.35–1.28)	0.22
≥2	0.77 (0.53–1.14)	0.20	0.67 (0.42–1.08)	0.10
BB				
Never used				
1	0.49 (0.28–0.86)	0.01[d]	0.45 (0.25–0.82)	0.01[d]
≥2	0.74 (0.52–1.04)	0.08	0.70 (0.48–1.03)	0.07

Abbreviations: ACE-I = angiotensin-converting enzyme inhibitor; AD = Alzheimer disease; ARB = angiotensin-1 receptor blocker; BB = β-blocker; BMI = body mass index; CCB = calcium channel blocker; CI = confidence interval; DBP = diastolic blood pressure; HR = hazard ratio; MCI = mild cognitive impairment; SBP = systolic blood pressure.
[a] ARB, diuretics, ACE-I, CCB, and BB were each used without concurrent use of any other type of antihypertensive medication.
[b] $p \leq 0.001$.
[c] $p \leq 0.005$.
[d] $p \leq 0.01$.

ARB, and ACE-I users, suggesting an additional beneficial effect of these antihypertensive medication groups on the risk of AD dementia.

There were a number of advantages of this study. First, our study included a large, well-characterized cohort, screened extensively to be free of baseline dementia. Second, medication use was visually validated and we had sufficient power to separate diuretic, ARB, ACE-I, CCB, or BB users by excluding those who reported concomitant use of any medications. However, we cannot account for effects of prior blood pressure levels, including severity, and for past medication use. The strength of exclusion of multiple antihypertensive medication users from our analysis may also be considered a weakness, because these may have had more severe HTN. Additionally, we were able to stratify medication user groups according to their mean SBP throughout the whole study, thus taking into account the effect of elevated SBP on the risk of AD.

This study also had limitations. Our study was a post hoc analysis; therefore, these data were not collected with our hypothesis as a primary outcome, thus it introduces biases. Our study population was highly educated and homogeneous for race, limiting generalizability. Although medications were visually inspected during visits, we could not accurately determine compliance and did not have information on prior use of these medications. As in all observational studies, our results may also be vulnerable to confounding. We sought to address confounding by adjusting for history of HTN, CHF, DM, and coronary artery disease, all of which are implicated in AD dementia and are main indications for use of diuretics, ARB, and ACE-I. Additionally, the study design introduced potential residual confounding because antihypertensive medication users may have received a diagnosis of vascular dementia in a larger proportion, which was addressed by evaluating associations between antihypertensive medication use and risk also for all-cause and vascular dementia. We found significant risk reduction among ARB and diuretic users in all-cause dementia, but none in vascular dementia (tables e-1 and e-2 on the *Neurology*® Web site at www.neurology.org). Another potential limitation is survival bias, because users of these medications might be more likely to die because of the increased mortality risk associated with HTN. However, this was addressed by performing a competing risk regression analysis between incidence of AD dementia and of death among diuretic, ARB, ACE-I, and no antihypertensive medication users, and we found similar incidence of death across the different groups, suggesting no competing risk of mortality. Because there is a large cost difference between ARB and other antihypertensive medications, we cannot rule out substantial residual confounding by socioeconomic status among ARB users, because our categories were based on income only. However, it was noted that diuretic, ARB, and BB users and those who did not use antihypertensive medication did not differ in terms of their income.

This post hoc longitudinal analysis found that diuretic, ARB, or ACE-I use was associated with reduced risk of AD among participants with normal cognition, with similar trends among participants with MCI. The consistent pattern of reduced risk of AD dementia associated with these medications warrants further, more mechanistic approaches, such as the use of imaging, to better understand the biological basis of these associations. This could lead to identification of pharmacologic targets for preventive interventions to slow cognitive decline and possibly delay progression to

AD dementia. This additional evidence could help the clinician choosing an antihypertensive medication based not only on blood pressure control, but also on additional benefits.

AUTHOR CONTRIBUTIONS

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. S. Yasar was responsible for the study concept and design, acquisition of data, statistical analysis and interpretation of data, drafting and critical revision of the manuscript, and study supervision. J. Xia was responsible for acquisition of data, statistical analysis and interpretation of data, drafting and critical revision of the manuscript. Dr. W. Yao was responsible for acquisition of data, statistical analysis and interpretation of data, and critical revision of the manuscript. Dr. C. Furberg was responsible for the study concept and design, interpretation of data, and critical revision of the manuscript. Dr. Q. Xue was responsible for the statistical analysis and interpretation of data, and critical revision of the manuscript. Dr. C. Mercado and Dr. A. Fitzpatrick were responsible for the acquisition of data, statistical analysis, and critical revision of the manuscript. Dr. L. Fried was responsible for the study concept and design, and critical revision of the manuscript. Dr. C. Kawas and Dr. K. Sink were responsible for the interpretation of data, and critical revision of the manuscript. Dr. J. Williamson was responsible for the study concept and design, acquisition of data, interpretation of data, drafting and critical revision of the manuscript. Dr. S. DeKosky was responsible for acquisition of data, interpretation of data, drafting and critical revision of the manuscript. Dr. M. Carlson was responsible for the study concept and design, acquisition of data, interpretation of data, drafting and critical revision of the manuscript, and study supervision.

ACKNOWLEDGMENT

The authors are indebted to Stephen Straus, MD, the late former director of the National Center for Complementary and Alternative Medicine (NCCAM), who championed efforts to evaluate complementary and alternative therapies in rigorous scientific fashion, and gratefully acknowledge the contribution of Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany, for their donation of the *Ginkgo biloba* tablets and identical placebos, in blister packs, for the study. The authors are also grateful to the volunteers, whose faithful participation made this longitudinal study possible. Pat Crowley, MS, Patricia Smith, Joyce Chabot, John Hopkins University, collected data, provided technical assistance, and supervision of personnel. Sharene Theroux, CCRP, Lisa Pastore, CCRP, University of California, Davis, collected data and provided technical assistance and supervision of personnel. Roberta Moyer, CMA, Cheryl Albig, CMA, University of Pittsburgh, collected data and provided technical assistance and supervision of personnel. Dee Posey, Margie Lamb, RN, Wake Forest University School of Medicine, collected data and provided technical assistance and supervision of personnel. Robert Hörr, MD, Joachim Herrmann, PhD, Schwabe Pharmaceuticals, provided drugs. Nancy Woolard, Kathryn Bender, PharmD, Susan Margitic, MS, Wake Forest University School of Medicine, provided technical assistance at the Clinical Coordinating Center. Elaine Cornell, UVM, University of Vermont, provided technical assistance at the Central Laboratory. Rose Jarosz, University of Pittsburgh, provided technical assistance at the MRI Reading Center. Richard Grimm, MD, PhD (Chair), University of Minnesota; Jonathan Berman, MD, PhD (Executive Secretary), National Center for Complementary and Alternative Medicine; Hannah Bradford, MAc, LAc, MBA, Carlo Calabrese, MD MPH, Bastyr University Research Institute; Rick Chappell, PhD, University of Wisconsin Medical School; Kathryn Connor, MD, Duke University Medical Center; Gail Geller, ScD, Johns Hopkins Medical Institute; Boris Iglewicz, PhD, Temple University; Richard S. Panush, MD, Department of Medicine Saint Barnabas Medical Center; and Richard Shader, PhD, Tufts University, served on the Data Safety Monitoring Board.

STUDY FUNDING

The study was sponsored by the Ginkgo Evaluation of Memory (GEM) Study and was supported by U01 AT000162 from the NCCAM and the Office of Dietary Supplements, and support from the National Institute on Aging, National Heart, Lung, and Blood Institute, the University of Pittsburgh Alzheimer's Disease Research Center (P50AG05133), the Roena Kulynych Center for Memory and Cognition Research, and the National Institute of Neurological Disorders and Stroke.

DISCLOSURE

S. Yasar has been funded by NIH grants 1U01AT00016207, 30AG021334, and DA10013, and received research support from the John A. Hartford Foundation, Nathan Shock Memorial Fund, Sanofi, and families of grateful patients (R. Borgatta and Alan Spiegel). She served as a consultant for Charles River Company. She also sees in her clinical practice people with memory disorders (25% effort) for which she bills. J. Xia has been funded by NIH grants P50AG05146, P30AG021334, R37AG19905, and P01AG027735; U01AT000162 and K23DC011279 grants. She received research support from Sanofi and families of grateful patients (R. Borgatta). W. Yao has been funded by NIH grants R01AG027236, P30AG021334, and P01AG027735. He has also received salary support from University of Pittsburgh subcontract award ID 0017285 (118549-1); University of California, Irvine subcontract award ID 2010-2530; and HHSF223201000072C (Food and Drug Administration). C. Furberg reports no disclosures. Q. Xue has been funded by NIH grants 1R03AG041992, P30AG021334, 5T35AG026758, R01AG040100, 1R21HS017650, 5P01AG027735, R37AG19905, as well as a subcontract from Canadian Institutes of Health Research (258866). C. Mercado has been funded by NIH grants U01AT00162, MH081757, and NIH/NHLBI-HC-08-10. A. Fitzpatrick has been funded by NIH grants HHSN268201200036C, N01HC85239, N01HC85079 through N01HC85086, N01HC35129, N01HC15103, N01HC55222, N01HC75150, N01HC45133, HL080295, HL80698, HL10431701A1, AG023629, AG15928, AG20098, AG027058, AG37790, AG033193, AT00162, AT006668, AT006668, ES019261, MH081757, Fogarty International Center TW008431, and Centers for Disease Control 5U48DP001911. She has also worked on a subcontract for analytic work from GlaxoSmithKline. L. Fried has been funded by NIH grants P30AG2133 and R37AG019905. C. Kawas has been funded by NIH grants R01AG21055, R01AG030753, R01AG304087, P50AG16573; and 18FAV45A014, Avid Radiopharmaceuticals, Inc. She is on the DSMC for Eli Lilly & Company, Biogen Idec MA, Inc., and Department of Veterans Affairs. She also sees in her clinical practice people with memory disorders (10% effort) for which she bills. K. Sink has been funded by NIH grants NS075107, HC0904, AG024904, AG022376, AG10483, WH1110, and HHSN271-2011-00004C, and investigator initiated grants from the Alzheimer's Association and the Donald W. Reynolds Foundation. She was the site principal investigator (PI) for a multicenter trial sponsored by Danone Research. She serves on the DSMB for the NIH funded COMET-AD trial. J. Williamson has been funded by NIH grants 1AT000162-00, P30AG21332, N01HC95182, N01HC95182, HHSN268200900040C, HHSN2682011, HSN 27100023C, and 1UO1AG02982401A2 and also grants from the Donald W. Reynolds and John A. Hartford Foundation. He is a DSMB member for the IRL-GREY trial (NINDS) and Coordinating Center PI for the cognitive assessment components of the ACCORD (NHLBI), SPRINT (NHLBI), and LIFE (NIA) clinical trials. S. DeKosky serves as a consultant for Helicon Therapeutics, Genzyme Corporation, and Lilly Pharmaceuticals. He is the site PI at the University of Virginia Memory Disorders Clinics for experimental therapeutic trials of Alzheimer disease medications for the following companies: Elan Pharmaceuticals, Novartis Pharmaceuticals, Janssen Pharmaceuticals, Pfizer Pharmaceuticals, and Baxter Pharmaceuticals. M. Carlson has been funded by NIH grants P01AG027735, U01DC007422, R01AG032317, U01HL096812, U01AG032947, P50AG005146, R56AG023629, and 5R01HL08029506, and the Alzheimer's Drug Discovery Foundation. Go to Neurology.org for full disclosures.

Received January 8, 2013. Accepted in final form April 22, 2013.

REFERENCES

1. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol 2005;4:487–499.
2. Farmer ME, Kittner SJ, Abbott RD, Wolz MM, Wolf PA, White LR. Longitudinally measured blood pressure,

antihypertensive medication use, and cognitive performance: the Framingham Study. J Clin Epidemiol 1990;43:475–480.
3. Guo Z, Fratiglioni L, Zhu L, Fastbom J, Winblad B, Viitanen M. Occurrence and progression of dementia in a community population aged 75 years and older: relationship of antihypertensive medication use. Arch Neurol 1999;56:991–996.
4. Khachaturian AS, Zandi PP, Lyketsos CG, et al. Antihypertensive medication use and incident Alzheimer disease: the Cache County Study. Arch Neurol 2006;63:686–692.
5. Haag MD, Hofman A, Koudstaal PJ, Breteler MM, Stricker BH. Duration of antihypertensive drug use and risk of dementia: a prospective cohort study. Neurology 2009;72:1727–1734.
6. Li NC, Lee A, Whitmer RA, et al. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. BMJ 2010;340:b5465.
7. Hoffman LB, Schmeidler J, Lesser GT, et al. Less Alzheimer disease neuropathology in medicated hypertensive than nonhypertensive persons. Neurology 2009;72:1720–1726.
8. Petrovitch H, White LR, Izmirilian G, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia Aging Study. Neurobiol Aging 2000;21:57–62.
9. Korf ES, White LR, Scheltens P, Launer LJ. Midlife blood pressure and the risk of hippocampal atrophy: the Honolulu Asia Aging Study. Hypertension 2004;44:29–34.
10. McGuinness B, Todd S, Passmore P, Bullock R. The effects of blood pressure lowering on development of cognitive impairment and dementia in patients without apparent prior cerebrovascular disease. Cochrane Database Syst Rev 2006;(2):CD004034.
11. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the hypertension in the very elderly trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol 2008;7:683–689.
12. Staessen JA, Thijs L, Richart T, Odili AN, Birkenhager WH. Placebo-controlled trials of blood pressure-lowering therapies for primary prevention of dementia. Hypertension 2011;57:e6–e7.
13. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA 1991;265:3255–3264.
14. Prince MJ, Bird AS, Blizard RA, Mann AH. Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults. BMJ 1996;312:801–805.
15. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) Trial. Lancet 1998;352:1347–1351.
16. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 2003;163:1069–1075.
17. Tervo S, Kivipelto M, Hanninen T, et al. Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. Dement Geriatr Cogn Disord 2004;17:196–203.
18. Solfrizzi V, Panza F, Colacicco AM, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. Neurology 2004;63:1882–1891.
19. Rozzini L, Vicini Chilovi B, Trabucchi M, Padovani A. Antihypertensive medications influence the rate of conversion from mild cognitive impairment to Alzheimer disease. Arch Neurol 2008;65:993–994.
20. DeKosky ST, Fitzpatrick A, Ives DG, et al. The Ginkgo Evaluation of Memory (GEM) Study: design and baseline data of a randomized trial of ginkgo biloba extract in prevention of dementia. Contemp Clin Trials 2006;27:238–253.
21. DeKosky ST, Williamson JD, Fitzpatrick AL, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA 2008;300:2253–2262.
22. Fitzpatrick AL, Fried LP, Williamson J, et al. Recruitment of the elderly into a pharmacologic prevention trial: the Ginkgo Evaluation of Memory Study experience. Contemp Clin Trials 2006;27:541–553.
23. Teng EL, Chui HC. The modified Mini-Mental State (3MS) Examination. J Clin Psychiatry 1987;48:314–318.
24. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association; 1994.
25. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. 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 1984;34:939–944.
26. Fournier A, Oprisiu-Fournier R, Serot JM, et al. 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 2009;9:1413–1431.
27. Kehoe PG, Passmore PA. The renin-angiotensin system and antihypertensive drugs in Alzheimer's disease: current standing of the angiotensin hypothesis? J Alzheimers Dis 2012;30:S251–S268.
28. Solfrizzi V, Scafato E, Frisardi V, et al. Angiotensin-converting enzyme inhibitors and incidence of mild cognitive impairment: the Italian Longitudinal Study on Aging. Age 2013;35:441–453.