

Angiotensin-Converting Enzyme Inhibitors and Cognitive Decline in Older Adults With Hypertension

Results From the Cardiovascular Health Study

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Background: Hypertension (HTN) is a risk factor for dementia, and animal studies suggest that centrally active angiotensin-converting enzyme (ACE) inhibitors (those that cross the blood-brain barrier) may protect against dementia beyond HTN control.

Methods: Participants in the Cardiovascular Health Study Cognition Substudy with treated HTN and no diagnosis of congestive heart failure (n=1054; mean age, 75 years) were followed up for a median of 6 years to determine whether cumulative exposure to ACE inhibitors (as a class and by central activity), compared with other anti-HTN agents, was associated with a lower risk of incident dementia, cognitive decline (by Modified Mini-Mental State Examination [3MSE]), or incident disability in instrumental activities of daily living (IADLs).

Results: Among 414 participants who were exposed to ACE inhibitors and 640 who were not, there were 158 cases of incident dementia. Compared with other anti-HTN drugs, there was no association between exposure to all ACE inhibitors and risk of dementia (hazard ratio [HR], 1.01; 95%

confidence interval [CI], 0.88-1.15), difference in 3MSE scores (-0.32 points per year; $P=.15$), or odds of disability in IADLs (odds ratio [OR], 1.06; 95% CI, 0.99-1.14). Adjusted results were similar. However, centrally active ACE inhibitors were associated with 65% less decline in 3MSE scores per year of exposure ($P=.01$), and noncentrally active ACE inhibitors were associated with a greater risk of incident dementia (adjusted HR, 1.20; 95% CI, 1.00-1.43 per year of exposure) and greater odds of disability in IADLs (adjusted OR, 1.16; 95% CI, 1.03-1.30 per year of exposure) compared with other anti-HTN drugs.

Conclusions: While ACE inhibitors as a class do not appear to be independently associated with dementia risk or cognitive decline in older hypertensive adults, there may be within-class differences in regard to these outcomes. These results should be confirmed with a randomized clinical trial of a centrally active ACE inhibitor in the prevention of cognitive decline and dementia.

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THE PREVALENCE OF ALZHEIMER disease (AD) in the United States is projected to increase to approximately 9 to 13 million by 2050.^{1,2}

Conservative estimates project that 2 new cases will be diagnosed every minute in the United States by then and that delaying the onset of dementia, even by 1 year, would have a substantial impact on public health, reducing the number of cases over 10 years by an estimated 210 000.² Hypertension (HTN) is an important risk factor for the development of dementia, of both the vascular and the Alzheimer types.³⁻⁵ Epidemiological data from large cohort studies have typically shown an association between the use of anti-HTN drugs and a lower risk of dementia.⁶⁻⁸ However, con-

trolled trials of commonly used classes of anti-HTN drugs (calcium channel blockers, β -blockers, diuretics, and angiotensin-converting enzyme [ACE] inhibitors) have yielded mixed results with respect to their protective effect on the incidence of dementia.⁹⁻¹² Also, a Cochrane meta-analysis found that blood pressure reduction (by all drug classes combined) was not significantly associated with a reduced risk of cognitive impairment or dementia.¹³ Therefore, it raises the question of whether a mechanism independent of (or in addition to) blood pressure lowering accounts for the variable protective effects on cognition that have been described.

Several lines of evidence support the hypothesis that ACE inhibitors may have benefits on cognition beyond blood pressure

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Group Information: A list of the principal investigators and institutions of the Cardiovascular Health Study can be found at <http://www.chs-nhlbi.org/pi.htm>.

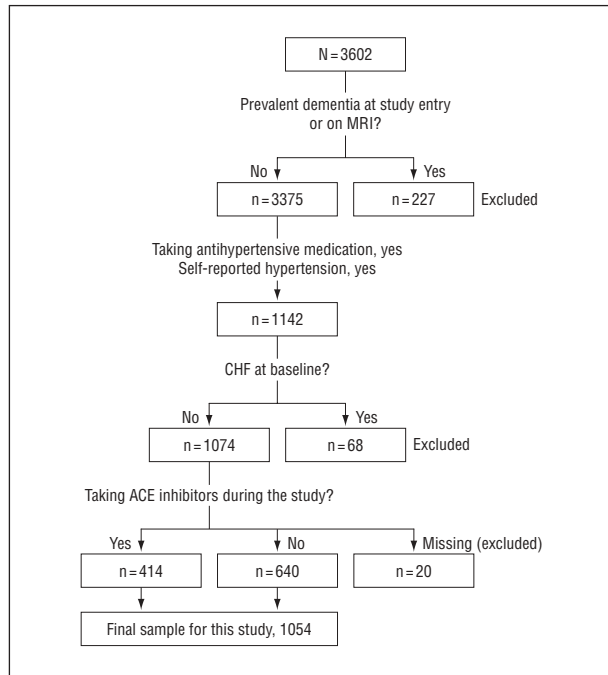


Figure. Sample population. ACE indicates angiotensin-converting enzyme; CHF, congestive heart failure; MRI, magnetic resonance imaging.

control. The brain is known to possess an intrinsic renin-angiotensin system that is involved in memory and cognition.¹⁴ Although specific mechanisms are unclear, stimulation of the renin-angiotensin system is involved in the activation of inflammatory cytokines that may play a role in degenerative dementias.^{15,16} A study in hypertensive rats found that lifetime treatment with captopril (an ACE inhibitor that crosses the blood-brain barrier), but not hydralazine, substantially attenuates the age-related impairment in learning and memory despite equal blood pressure control in the 2 groups.¹⁷ These results support the contention that the mechanism of preservation of learning and memory may not be primarily attributable to the blood pressure-lowering effect of captopril.

Using a large, population-based cohort, we aimed to determine (1) whether ACE inhibitors as a class, compared with other anti-HTN agents, confer a lower risk of incident dementia, cognitive decline, or incident disability in instrumental activities of daily living (IADLs) among older adults with HTN, and (2) whether there is a difference between ACE inhibitors that cross the blood-brain barrier (centrally active) and those that do not (noncentrally active). We hypothesized that centrally active ACE inhibitors, but not noncentrally active ones, would be associated with a lower risk of incident dementia, cognitive decline, and disability in IADLs compared with other anti-HTN drugs.

METHODS

PARTICIPANTS AND STUDY DESIGN

These analyses use longitudinal data from the Cardiovascular Health Study (CHS), a prospective multicenter, population-based cohort study of cardiovascular risk factors in 5888 community-dwelling older adults. An ancillary study was con-

ducted to evaluate the incidence and prevalence of dementia in a subset of the cohort (Cardiovascular Health Cognition Substudy, 3602 participants) who underwent brain magnetic resonance imaging (MRI) between 1991 and 1994.^{18,19} Participants were evaluated at baseline with clinical assessments that included physical, cognitive, and functional assessments as well as laboratory testing. Medication, function, cognitive, physical examination, and medical history data were updated at annual participant visits. For this analysis, participants who were determined to have prevalent dementia at the time of the MRI (defined as “baseline” for these analyses) were excluded. To limit confounding by indication, we also restricted our analyses to participants who had treated HTN, defined as self-reported HTN, and were taking an anti-HTN medication. Because ACE inhibitors are also commonly used for congestive heart failure (CHF) treatment and because CHF may impair cognition, we further excluded patients with CHF at baseline. After applying these entry and exclusion criteria, 1054 participants formed our study population (**Figure**).

PREDICTOR/EXPOSURE

The predictor of interest was cumulative exposure to ACE inhibitors. Participants brought in all medications used in the prior 2 weeks, and each one was recorded by study staff. The ACE inhibitors were classified into 2 groups according to their ability to cross the blood-brain barrier. These determinations were made based primarily on experiments in rats. The 2 most common means of measuring ability to cross the blood-brain barrier were (1) analysis of ground-up, tissue-specific ACE activity after administration of ACE inhibitors orally or subcutaneously, and (2) tissue-specific imaging of a radiolabeled ACE inhibitor after administration of various ACE inhibitors (which compete for binding with the radiolabeled ACE inhibitor). After review of the literature and pharmaceutical package inserts, captopril, fosinopril, lisinopril, perindopril, ramipril, and trandolapril were classified as crossing the blood-brain barrier (centrally active), while benazepril, enalapril, moexipril, and quinapril were classified as not (noncentrally active).²⁰⁻²⁸ If data on the use of ACE inhibitors were missing for an examination and the values before and after that examination agreed, the missing value was replaced with the value observed for those visits. If data for more than 2 visits were missing, no imputations of missing data were attempted. Only 1.3% of the values were imputed.

OUTCOMES

For the purposes of follow-up, the start of the study was defined for each participant as the year when he or she underwent MRI, and the end of the study was defined as the date of dementia diagnosis, his or her last evaluation in 1999, or lost to follow-up, whichever came first. Because HTN is a risk factor for both Alzheimer dementia and vascular dementia,³⁻⁵ the sum of which accounted for more than 96% of incident dementia cases in the CHS,¹⁹ time-to-incident, all-cause dementia was the primary outcome. Participants at high risk for dementia based on prespecified criteria¹⁸ and all minority participants underwent detailed evaluations. After clinical evaluation, neuropsychiatric testing, and an MRI scan, the diagnosis of dementia was adjudicated by a committee of neurologists and psychiatrists and has been extensively described elsewhere.^{18,19}

Prespecified secondary outcomes included change in cognition over time as measured by the Modified Mini-Mental State Examination (3MSE)²⁹ and dependence in IADLs.³⁰ Both of these outcomes, measured annually, are correlated with dementia and may pick up deficits in cognition before a diagnosis of demen-

tia is made. The 3MSE is a 100-point test of global cognition similar to the Folstein Mini-Mental State Examination, with higher scores indicating better performance. Six IADLs were measured (shopping, meal preparation, money management, telephone use, light housework, and heavy housework) and scored as independent (0) or dependent (1) and summed. For this analysis, we dichotomized participants as completely independent or dependent in 1 or more IADLs. We excluded participants with dependencies in IADLs at baseline (n=252).

COVARIATES

Potential confounders of the relationship between ACE inhibitor use and cognition were considered. Demographics included age, sex, race (classified as white vs other), education (classified as less than high school, high school, and more than high school), and income (categorized as <\$12 000/y, \$12 000-34 999/y, or ≥\$35 000/y). Health-related behaviors included smoking status (never, former, or current smoker), alcohol consumption per week (none, 1-7 drinks, and >7 drinks), and exercise (kilocalories per week expended). We also considered baseline comorbidities, including diabetes (classified as none, impaired fasting glucose levels, and diabetes), coronary artery disease, history of stroke, renal insufficiency (using the baseline serum creatinine level as a surrogate measure), hyperlipidemia (using the baseline serum low-density lipoprotein level as a surrogate measure), inflammation (using C-reactive protein level as a surrogate measure), and depression (measured with the Center for Epidemiologic Studies–Depression Scale³¹ annually). Measures of dementia risk, including baseline 3MSE scores and apolipoprotein E ε4 allele status (presence or absence of an ε4 allele) were also obtained. Systolic blood pressure, incident stroke, and any other anti-HTN medication use were recorded at annual visits.

STATISTICAL ANALYSES

Bivariate analyses were performed to determine the associations between covariates of interest and exposure to ACE inhibitors as well as incident dementia. Continuous variables were examined with *t* tests, and categorical variables were examined using the χ^2 test. Covariates that were not associated ($P > .10$) with either the predictor (exposure to ACE inhibitors) or the outcome (incident dementia) were not included in our multivariate models. Those variables included exercise and C-reactive protein level. Apolipoprotein E ε4 was used not as a covariate, but was considered as a potential effect modifier in the relationship between ACE inhibitors and incident dementia. No interaction was found; therefore, the analyses were ultimately not stratified by apolipoprotein E ε4 status.

Time-dependent proportional hazards regression analyses were used to model the relationship of time to dementia and exposure to ACE inhibitors (total years of ACE inhibitor use). Exposure to ACE inhibitors was recorded longitudinally. At each follow-up, exposure to ACE inhibitors was defined as the total number of years the participant had been taking ACE inhibitors up to the year before the current follow-up (cumulative exposure, 1-year lag). For example, an individual who survived (not demented) after 6 years and had ACE inhibitor use at baseline and at years 3 and 4 but not at years 1, 2, and 5 would have a cumulative exposure to ACE inhibitors that equals 1 up to the beginning of year 3, equal to 2 up to the beginning of year 4, and equal to 3 up to the beginning of year 6. We adjusted for potential confounders (described above) in a stepwise fashion, including baseline demographics, health-related behaviors, comorbidities and laboratory test results; and baseline 3MSE score. We also controlled for time-dependent covariates, including incident stroke, systolic blood pressure, de-

pression scores, and use of other anti-HTN drugs annually at each follow-up. We adjusted for the use of other anti-HTN drugs at each visit because we were interested in knowing what impact ACE inhibitors had on dementia risk (or other outcomes) independent of the use of other anti-HTN agents. Although we restricted our population to treated patients with HTN and excluded those with CHF at baseline, we further attempted to avoid confounding by indication for ACE inhibitors by censoring participants at the time that a new CHF diagnosis was made. Because dementia is insidious in its onset, exposures thought to be protective would need to be present well before the diagnosis. Therefore, we incorporated a 1-year lag between exposure and outcome.³² Results are presented as hazards ratios (HRs) and 95% confidence intervals (CIs) providing the relative risk for an increase of 1 year of ACE inhibitor exposure, with the reference group comprising participants who entered the study taking an anti-HTN drug but who were not yet exposed to ACE inhibitors. Proportional hazards assumptions for ACE inhibitor use were tested and met.³³

Because we hypothesized, a priori, that ACE inhibitors that cross the blood-brain barrier would have a different effect than those that do not, further analyses were conducted to compare the risk of dementia for centrally active and noncentrally active ACE inhibitors as cumulative, time-dependent predictors, again with participants who were not yet exposed to ACE inhibitors as the reference group. The statistical models were fitted as those described above except that 2 predictor variables were now included: cumulative exposure to centrally active ACE inhibitors and cumulative exposure to noncentrally active ACE inhibitors. In sensitivity analyses, we also examined exposure to the subclasses of ACE inhibitors as time-dependent covariates (yes or no each year, rather than cumulative exposure) to assess the effect of current exposure on cognitive performance.

The association between cumulative exposure to ACE inhibitors and change in 3MSE scores over time was modeled using mixed-effects models. The predictor variable was the same as in time-dependent proportional hazards models, and the same set of covariates was used to build the adjusted model, with the exception of the baseline 3MSE score. The effects of centrally active and noncentrally active ACE inhibitors were similarly modeled by including 2 predictors in the model. Autoregressive (1) structure was used to account for within-subject correlation of scores over time. The results are presented as the change in 3MSE score (points) associated with every 1 additional year of exposure to ACE inhibitors as compared with nonexposure. Sensitivity analyses were also performed as described above.

For the IADL disability outcome, annual IADL scores were recoded as binary outcomes (0 vs 1 or more) as described previously. Only the patients whose IADL scores were 0 at baseline were included in this analysis. A generalized estimating equations model with repeated binary response was fitted to assess the association between cumulative exposure to ACE inhibitors and incident disability in IADLs. The same set of covariates was used to fit the adjusted model as was used with the incident dementia outcome, and a 1-year lag was again imposed. Autoregressive (1) structure was used to account for within-subject correlation. Results are presented as odds ratios (ORs) and 95% CIs and represent the odds of being disabled in IADLs for every year of exposure to ACE inhibitors as compared with nonexposure. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

The average age of participants at baseline was 75 years. Approximately 64% were women and 76% were white.

Table 1. Baseline Characteristics of 1054 Cardiovascular Health Study Participants by Exposure to ACE Inhibitors Followed Up for 5255 Person-Years

Variable	Ever ACE Inhibitor (n=414)	Never ACE Inhibitor (n=640)	P Value
Age, mean (SD), y	74.5 (4.7)	75.0 (5.0)	.10
Female, %	57.5	67.8	<.001
White race, %	76.6	76.1	.86
Education level, %			.57
Less than high school	25.9	27.2	
High school	31.6	28.6	
More than high school	42.5	44.2	
Income per year, \$.002
<12 000	19.2	29.4	
12 000-34 999	57.2	50.3	
≥35 000	23.5	20.3	
Smoking status, %			.74
Never	47.1	49.4	
Former	45.6	43.2	
Current	7.4	7.3	
Alcohol use, %			.13
None	54.0	57.9	
1-7 drinks/wk	33.9	33.7	
>7 drinks/wk	12.1	8.5	
3MSE score, mean (SD)	92.5 (5.7)	92.0 (6.5)	.06
CES-D score, mean (SD)	5.3 (4.9)	5.0 (4.7)	.28
Creatinine, mean (SD), mg/dL	1.1 (0.3)	1.0 (0.3)	.01
C-reactive protein, mean (SD), mg/L	5.7 (9.0)	5.8 (9.7)	.88
LDL, mean (SD), mg/dL	129.3 (35.1)	125.8 (32.5)	.10
≥1 APOE-ε4 allele, %	22.6	25.2	.35
Diabetes, %			<.001
None	69.4	80.1	
Impaired fasting glucose	8.0	8.3	
Diabetes	22.6	11.6	
Coronary artery disease, mean (SD)	17.4	19.4	.42
Systolic blood pressure, mean (SD), mm Hg	146.1 (22.8)	138.9 (19.5)	<.001
History of stroke, %	5.1	5.0	.96
Aspirin use, %	35.8	37.7	.53

Abbreviations: ACE, angiotensin-converting enzyme; APOE, apolipoprotein E; CES-D, Center for Epidemiologic Studies-Depression Scale; LDL, low-density lipoprotein; 3MSE, Modified Mini-Mental State Examination.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; C-reactive protein to nanomoles per liter, multiply by 9.524; LDL to millimoles per liter, multiply by 0.0259.

Those who had ever been exposed to ACE inhibitors during the study period (n=414) were more likely to be male, to have a higher income, to drink more than 7 drinks per week, to have higher creatinine and low-density lipoprotein values, and to have higher systolic blood pressure levels and were more than twice as likely to have diabetes at baseline (**Table 1**). Of the 414 participants who were exposed to ACE inhibitors, 224 took only centrally active ACE inhibitors, 138 took only noncentrally active ACE inhibitors, and 45 took both (at different times) over the course of the study. The characteristics of participants who took centrally active vs noncentrally active ACE inhibitors were similar, except that those tak-

ing centrally active ACE inhibitors had slightly higher baseline 3MSE scores (93.2 and 91.7 points, respectively; $P=.02$). Over a median follow-up of 6 years (interquartile range, 5-6 years), the mean (SD) exposure to ACE inhibitors was 3.24 (1.90) years; specifically to centrally active, it was 3.06 (1.83) years, and to noncentrally active, it was 2.70 (1.78) years. Approximately 38% of ACE inhibitor users were continuous users throughout the study period, with no difference in the length of continuous use between those taking centrally active ACE inhibitors and those taking noncentrally active ACE inhibitors.

INCIDENT DEMENTIA

There were 158 incident cases of dementia (101 Alzheimer, 21 vascular, 30 mixed Alzheimer and vascular, and 6 other causes). Of the 158 incident cases, 111 occurred in participants who were never exposed to ACE inhibitors (followed up for 3599 person-years) and 47 occurred in participants who had been exposed to ACE inhibitors (followed up for 1656 person-years once exposed to ACE inhibitors). Among older adults with HTN who were receiving drug therapy, we found no difference in the risk of dementia for users of ACE inhibitors (as a class) compared with other anti-HTN drug users (adjusted HR, 1.01; 95% CI, 0.87-1.18). However, when examined separately by blood-brain barrier-crossing status, exposure to ACE inhibitors that did not cross the blood-brain barrier was associated with a greater risk of dementia by 20% per year of exposure compared with non-ACE inhibitor users (adjusted HR, 1.20; 95% CI, 1.00-1.43). Given an average of approximately 3 years of exposure, this finding translates into an HR of 1.73 over 3 years. **Table 2** shows the results of the stepwise model building. There was very little change in HRs regardless of the covariates added. The results of sensitivity analyses, in which exposures to the subclasses of ACE inhibitors were examined as time-dependent covariates (measuring current exposure rather than cumulative exposure), were qualitatively similar to those of the primary analyses; however, the results were not statistically significant in multivariate adjusted models (HR, 1.10 [95% CI, 0.61-1.99] for ACE inhibitors not crossing the blood-brain barrier; and HR, 1.03 [95% CI, 0.61-1.73] for ACE inhibitors crossing the blood-brain barrier).

CHANGE IN 3MSE SCORES

We measured 3MSE scores over time as a measure of cognitive decline that might be more sensitive to change than an incident dementia diagnosis. The adjusted mean change in 3MSE scores was -0.45 points per year for participants taking anti-HTN drugs other than ACE inhibitors. When examined as a class, for every year of exposure to ACE inhibitors compared with other anti-HTN drugs, there was no significant difference in decline in 3MSE scores (-0.28 points per year; $P=.09$). However, when examined by blood-brain barrier-crossing status, the use of ACE inhibitors that cross the blood-brain barrier compared with other anti-HTN drugs was associated with 65% less decline per year of exposure (-0.16

Table 2. Risk of Incident Dementia per Year of Exposure to ACE Inhibitors (as a Class) and by Blood-Brain Barrier–Crossing Status of the ACE Inhibitor^a

Model	All ACE Inhibitors		Centrally Active ACE Inhibitors		Noncentrally Active ACE Inhibitors	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Unadjusted	1.01 (0.88-1.15)	.90	0.89 (0.74-1.08)	.25	1.18 (1.00-1.39)	.05
Plus demographics, health behaviors, and comorbidities/laboratories ^b	1.05 (0.91-1.21)	.52	0.91 (0.73-1.13)	.41	1.23 (1.03-1.46)	.02
Above plus time-dependent systolic BP and incident stroke	1.05 (0.91-1.22)	.50	0.92 (0.74-1.14)	.43	1.23 (1.03-1.47)	.02
All above plus other HTN medications	1.01 (0.87-1.18)	.86	0.88 (0.70-1.09)	.24	1.20 (1.00-1.43)	.05

Abbreviations: ACE, angiotensin-converting enzyme; BP, blood pressure; CI, confidence interval; HR, hazard ratio; HTN, hypertension.

^aThe reference group comprises users of other anti-HTN drugs in both analyses.

^bAge, sex, race, education level, income, smoking status, alcohol use, diabetes, coronary artery disease, serum creatinine level, serum low density lipoprotein level, 3MSE score, and time-dependent depression score.

Table 3. Change in Modified Mini-Mental State Examination Score (3MSE) (Points per Year of Exposure to ACE Inhibitors)^a

Variable	Unadjusted			Adjusted ^b		
	3MSE	SE	P Value ^c	3MSE	SE	P Value ^c
Other antihypertensive drugs (reference)	-0.49	0.07		-0.45	0.06	
ACE inhibitors (all)	-0.32	0.11	.15	-0.28	0.09	.09
Centrally active ACE inhibitors	-0.22	0.13	.06	-0.16	0.11	.01
Noncentrally active ACE inhibitors	-0.52	0.17	.83	-0.53	0.15	.60

Abbreviation: ACE, angiotensin-converting enzyme.

^aIn separate models, we examined all ACE inhibitors vs reference and centrally vs noncentrally active vs reference. The reference group was the same in both models.

^bAdjusted for age, sex, race, education level, income, smoking status, alcohol use, diabetes, coronary artery disease, serum creatinine level, and serum low density lipoprotein level at baseline as well as depression score, systolic blood pressure, history of stroke, and other hypertension drug use annually.

^cThe P values listed reflect a comparison with the reference group.

Table 4. Odds of IADL Disability per Year of Exposure to ACE Inhibitors^a

Variable	Unadjusted		Adjusted ^b	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Other antihypertensive drugs	1 [Reference]		1 [Reference]	
ACE inhibitors (all)	1.06 (0.99-1.14)	.09	1.10 (1.02-1.20)	.02
Centrally active ACE inhibitors	1.03 (0.95-1.13)	.44	1.07 (0.97-1.18)	.16
Noncentrally active ACE inhibitors	1.11 (1.00-1.23)	.05	1.16 (1.03-1.30)	.01

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; IADL, instrumental activities of daily living; OR, odds ratio.

^aIn separate models, we examined all ACE inhibitors vs reference and centrally vs noncentrally active vs reference. The reference group was the same in both models.

^bAdjusted for age, sex, race, education level, income, smoking status, alcohol use, diabetes, coronary artery disease, serum creatinine level, serum low density lipoprotein level, and Modified Mini-Mental State Examination score at baseline as well as depression score, systolic blood pressure, history of stroke, and other hypertension drug use annually.

points per year; $P = .01$) (**Table 3**). The results of the sensitivity analyses using time-dependent ACE inhibitor exposure were qualitatively similar but not statistically significant in multivariate adjusted models ($P = .21$).

IADL DISABILITY

For every year of exposure to ACE inhibitors as a class compared with other anti-HTN drugs, we found a greater odds (OR, 1.10; 95% CI, 1.02-1.20; $P = .02$) of IADL disability. However, when examined by ability to cross the blood-brain barrier, it was exposure to noncentrally ac-

tive ACE inhibitors that was associated with the greater risk. For every year of exposure to those ACE inhibitors, there is a 1.16 greater odds of being dependent in at least 1 IADL (95% CI, 1.03-1.30; $P = .01$) (**Table 4**).

COMMENT

In a large, well-characterized cohort of treated older adults with HTN who were followed up for a median of 6 years, duration of exposure to ACE inhibitors as a class vs other anti-HTN classes was not associated with a reduction in

the risk of dementia. However, when examined by central activity, exposure to ACE inhibitors that do not cross the blood-brain barrier was associated with a 73% greater risk of incident dementia and a 56% greater risk of incident IADL disability over 3 years of exposure compared with other anti-HTN agents. In contrast, exposure to ACE inhibitors that do cross the blood-brain barrier was associated with a 65% reduction in cognitive decline per year of exposure as measured by the 3MSE. Qualitatively, the direction of results for all outcomes favored ACE inhibitors that cross the blood-brain barrier.

The finding that the association of ACE inhibitors with cognition depends on whether the drug crosses the blood-brain barrier was also reported by Ohru et al,³⁴ who found no difference in the incidence of AD (n=90 cases) in Japanese patients who were taking various types of anti-HTN drugs but did find a significantly lower risk of AD in a subgroup analysis of ACE inhibitors that cross the blood-brain barrier (captopril and perindopril) vs those that do not (enalapril and imidapril). No data on cognitive scores or functional status were reported. Improvement in cognitive function, independent of blood pressure control, has also been shown with the angiotensin II receptor blocker losartan, which crosses the blood-brain barrier.³⁵ However, in the SCOPE trial, participants receiving candesartan-based anti-HTN therapy were no less likely to develop dementia than participants receiving other classes of anti-HTN medications.¹² In secondary analyses of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), there was not a significant reduction in the incidence of all-cause dementia among patients who were assigned to perindopril therapy (centrally active ACE inhibitor), but there was a reduced risk of cognitive decline (defined by decline in Mini-Mental State Examination score).¹¹ The CHS population in the present study differs from that of PROGRESS in that all participants in PROGRESS had a cerebrovascular accident before entry into the study.

There is biologic plausibility for why centrally active ACE inhibitors may benefit cognition. For example, in addition to the anti-inflammatory actions of ACE inhibitors as a mechanism for the reduced cognitive decline that was discussed in the introduction, several other mechanisms are also plausible. First, there are increased concentrations of ACE, angiotensin II, and angiotensin I receptors in the cerebral cortex of patients with AD,^{36,37} and angiotensin II has been shown to inhibit acetylcholine release in rats and humans.^{38,39} Therefore, blocking ACE activity with a centrally active ACE inhibitor could decrease angiotensin II levels, potentially reducing the inhibitory action on acetylcholine release and thereby increasing acetylcholine concentration. This mechanism may relate more to the acute effects of central ACE inhibition on cognitive testing (such as 3MSE) than to long-term dementia risk. There is also microvascular pathology and decreased cerebral blood flow in AD.⁴⁰ Angiotensin II is a vasoconstrictor, and an increase in perivascular staining for ACE and angiotensin II has been shown in patients with AD.³⁶ Thus, centrally active ACE inhibitors may improve cerebral blood flow. On the other hand, a recent study showed that ACE may be important in converting β -amyloid₁₋₄₂ into β -amyloid₁₋₄₀ and that ACE in-

hibitors block this process and increase β -amyloid₁₋₄₂ deposition in the brains of mice.⁴¹ These results suggest that ACE inhibitors that cross the blood-brain barrier might increase the risk of AD. The net effects of these potentially opposing mechanisms should be determined in a randomized trial.

In this study, exposure to ACE inhibitors that do not cross the blood-brain barrier was associated with a greater risk of incident dementia and IADL disability (which are primarily cognitive tasks) when compared with other classes of anti-HTN drugs. While there is biologic plausibility for the reduction in cognitive decline seen among patients taking centrally active ACE inhibitors, why would noncentrally active ACE inhibitors be associated with a greater risk of dementia and IADL disability? While it is possible that noncentrally active ACE inhibitors are harmful, it is more likely that they are simply less helpful in the prevention of dementia and IADL disability than other anti-HTN drug classes combined. Angiotensin-converting enzyme inhibitors may be less effective in reducing the risk of selected blood pressure-related complications than other blood pressure-lowering drugs, and, perhaps most pertinently to cognition, the risk of stroke remains higher than when other classes of anti-HTN agents are used.^{42,43} These previous studies support the possibility that the effects of different agents on cognition might differ. Similarly, our results support the hypothesis that the centrally active ACE inhibitors are associated with a lower risk of cognitive decline via mechanisms other than blood pressure control. A difference in the brain mechanisms of centrally and noncentrally active ACE inhibitors may account for some of the variable trial results with respect to ACE inhibitors and cognition. The results of the sensitivity analyses using time-dependent, current exposure to ACE inhibitor subclasses were consistent with the directions of associations in our primary analyses but were not statistically significant and may be interpreted as providing insight that is more relevant to the association of acute exposures than to those of chronic or cumulative exposures. When interpreted in the context of our primary results, these additional analyses provide support for the contention that cumulative (or chronic) exposure to ACE inhibitor subclasses may be more strongly associated with the risk of dementia and cognitive decline than is acute exposure.

While this study is based on a large, well-characterized cohort with extensive cognitive follow-up and subclinical disease markers, there are several methodological limitations to highlight. As with all pharmacoepidemiology studies, it is impossible to rule out confounding by indication entirely. However, we limited the effect of this type of confounding by methods of restriction and adjustment.⁴⁴ We restricted our analyses to treated patients with HTN; therefore, everyone had an indication for an ACE inhibitor. Furthermore, we excluded persons with the other main indication for ACE inhibitors, CHF, and censored individuals if they developed CHF during the study. While patients with HTN and diabetes are more likely to receive ACE inhibitors, we did control for diabetes in the analyses. Since diabetes is associated with cognitive decline, an increased proportion of diabetics among ACE inhibitor users would not explain the reduced risk of cognitive de-

cline seen with ACE inhibitors that cross the blood-brain barrier. Also, it is unlikely that physicians consider whether ACE inhibitors cross the blood-brain barrier when selecting which ACE inhibitor to prescribe; therefore, it is unlikely that confounding by indication could explain the results. In addition to confounding by indication, there could also be residual confounding from other factors. While CHS has a rich set of clinical measures and biomarkers, many of which we controlled for, there is always the possibility of residual confounding.

Treatment-related imbalances in loss to follow-up among patients becoming cognitively impaired has also been cited as a potential source of bias in clinical trials measuring cognition as an outcome.⁴⁵ There were no substantial differences in loss to follow-up among categories of ACE inhibitor use in this study. The classification of centrally and noncentrally active ACE inhibitors was predominantly based on basic science animal data because human data were generally lacking, and because of variable methods of measurement, we were unable to provide units of measure for degrees of central activity. Furthermore, while a compound's ability to cross the blood-brain barrier largely depends on its size, charge, and lipophilicity, the integrity of the blood-brain barrier and the dose of the medication could influence its central activity. However, if there was misclassification (ie, drugs classified as not centrally active did actually cross the blood-brain barrier), we would have expected it to bias the results toward the null. Another potential source of misclassification bias of the exposure is that we do not know what the exposure to ACE inhibitors was before baseline. However, this type of bias likely affects few participants since ACE inhibitor use did not gain momentum until the late 1980s (only 10% of anti-HTN users were taking ACE inhibitors in 1988).⁴⁶ We could not account for the timing of ACE inhibitor exposure. For example, our models treated 3 years of exposure to ACE inhibitors the same, regardless of whether the exposure occurred early or late in the study. We do note, however, that approximately 40% of ACE inhibitor users were continuous users throughout the study period and that the median duration of use did not differ between users of centrally and noncentrally active ACE inhibitors. There were few cases of dementia that were not attributable to AD; therefore, we could not separate our analyses by dementia type. Further studies are needed to determine whether the effects of ACE inhibitors on cognition and dementia risk are the same for the most common dementia subtypes.

The potential public health impact of these findings is significant given the burden of cognitive impairment-related disability, the high prevalence of HTN, and the potential impact that the choice of agents to manage HTN may have beyond blood pressure control and cardiovascular disease risk. Based on the results of this study, compared with other anti-HTN drug classes, the use of noncentrally active ACE inhibitors (independent of use of other anti-HTN drugs) was associated with an approximately 56% greater risk of IADL disability and a 73% greater risk of dementia after 3 years of exposure. Conversely, the use of centrally active ACE inhibitors was associated with 65% slower cognitive decline on a global

measure of cognition. While these results come from an observational study and should be confirmed with a randomized, controlled trial of the use of a centrally active ACE inhibitor in the prevention of cognitive decline and dementia, it would appear that there may be within-class differences in the association of ACE inhibitors and cognition.

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