Antihypertensive Medication Use and Incident Alzheimer Disease

The Cache County Study

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Background: Recent reports suggest that antihypertensive (AH) medications may reduce the risk of dementing illnesses.

Objectives: To examine the relationship of AH medication use with incidence of Alzheimer disease (AD) among the elderly population (aged 65 years and older) of Cache County, Utah, and to examine whether the relationship varies with different classes of AH medications.

Methods: After an initial (wave 1) multistage assessment (1995 through 1997) to identify prevalent cases of dementia, we used similar methods 3 years later (wave 2) to identify 104 incident cases of AD among the 3308 survivors. At the baseline assessment, we obtained a detailed drug inventory from the study participants. We carried out discrete time survival analyses to examine the association between the use of AH medications (including angiotensin converting enzyme inhibitors, β-blockers, calcium channel blockers, and diuretics) at baseline with subsequent risk of AD.

Results: Use of any AH medication at baseline was associated with lower incidence of AD (adjusted hazard ratio, 0.64; 95% confidence interval, 0.41-0.98). Examination of medication subclasses showed that use of diuretics (adjusted hazard ratio, 0.57; 95% confidence interval, 0.33-0.94), and specifically potassium-sparing diuretics (adjusted hazard ratio, 0.26; 95% confidence interval, 0.08-0.64), was associated with the greatest reduction in risk of AD. Corresponding analysis with a fully examined subsample controlling for blood pressure measurements did not substantially change our findings.

Conclusions: These data suggest that AH medications, and specifically potassium-sparing diuretics, are associated with reduced incidence of AD. Because the latter association is a new finding, it requires confirmation in further study.

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HIGH BLOOD PRESSURE MAY increase the risk of Alzheimer disease (AD).1-6 Several observational and experimental studies have therefore evaluated the potential of antihypertensive (AH) medications for modification of the risk of AD.

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Results on this point from several longitudinal, population-based studies remain equivocal. The Kungsholmen Project found a lower rate of incident AD in participants taking AH medications, notably diuretics, at baseline.7,8 but the Rotterdam study9 found that AH medication users had reduced risk of incident vascular dementia but not AD. Two other observational studies10,11 examined performance over time on standardized neurocognitive tests and found lower risk of cognitive decline among treated vs untreated hypertensive subjects.

Several randomized trials for the prevention of cardiovascular disease have included cognitive measures as secondary end points. Three such trials, the Systolic Hypertension in the Elderly Project (SHEP), the Medical Research Council (MRC) trial, and Study on Cognition and Prognosis in the Elderly (SCOPE), showed no benefit in cognitive performance among participants receiving β-adrenergic blockers, thiazide diuretics, or angiotensin II type 1 receptor blockers.12-14 By contrast, both the Heart Outcomes Prevention Evaluation (HOPE) Study15 and the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)16 found a 41% reduction in cognitive decline associated with stroke and a 34% reduction in dementia among patients with recurrent...
stroke, respectively, with the use of an angiotensin converting enzyme (ACE) inhibitor (in combination with a diuretic if indicated). Finally, the Systolic Hypertension in Europe (Syst-Eur) trial and the open label extension\textsuperscript{17,18} showed that nitrendipine, a calcium channel antagonist, reduced the incidence of dementia (mostly AD) by nearly 50\% as compared with placebo.

Using data from the Cache County Study, we sought further evidence of the relationship between AH medication use and risk of AD. Specifically, we investigated whether protective effects, if any, were specific to individual classes of AH medications.

**METHODS**

**STUDY OVERVIEW**

The Cache County Study is an ongoing investigation of dementing illnesses among the elderly population of Cache County, Utah. Its methods have been described in detail elsewhere\textsuperscript{19,20} Briefly, in 1995 we approached all elderly (aged 65 years or older) permanent residents of Cache County (wave 1). We obtained buccal DNA from 97\% of participants for determination of genotype of the polymorphic locus that encodes apolipoprotein E, \textit{APOE}\textsubscript{\textepsilon}/H9252, and we administered a standardized interview to all participants. The interview covered a range of potential risk and protective factors for dementia, including medication history. We then used a multistage procedure, described later in this article, to identify and diagnose prevalent cases of dementia. This procedure included full examination of a 19\% age-, sex-, and \textit{APOE} genotype-stratified subsample of the population, irrespective of screening results. Three years later, beginning in 1998, we carried out a second set of assessments (wave 2) using similar methods to detect incident cases of dementia among living participants who had not been demented at wave 1.

**EXPOSURE ASSESSMENT**

Interviews at both wave 1 and wave 2 included a detailed inventory of all over-the-counter and prescription medications in current use. These inventories relied on a visual inspection of all available medication vials. When participants were institutionalized, we obtained this information from nursing home medication records. Community-dwelling participants were asked further questions about the form, dosage, start date, and duration of medication use. We then classified non-demented wave 1 participants as AH drug users if they were currently taking any of the following drug classes: ACE inhibitors, $\beta$-blocking antiadrenergics ($\beta$-blockers), calcium ion channel blockers, and diuretics. We further categorized calcium channel blockers into dihydropyridine types (nimodipine, nifedipine, nicardipine hydrochloride, isradipine, felodipine, amlodipine besylate, and nisoldipine) and others (verapamil hydrochloride, nicardipine hydrochloride, diltiazem hydrochloride) and categorized diuretics as thiazides (chlorothiazide, chlorthalidone, hydrochlorothiazide, indapamide, methyclothiazide, metolazone, polythiazide), potassium-sparing agents (spironolactone, triamterene, amiloride hydrochloride), or loop diuretics (furosemide, ethacrynic acid, bumetanide).

**OUTCOME ASSESSMENT**

Screening and assessment procedures for dementia have been described in detail elsewhere\textsuperscript{9,10,23} Briefly, screening began with an in-person interview that included an adaptation of the Modified Mini-Mental State Examination (3MS)\textsuperscript{21} or, for those unable to participate, the Informant Questionnaire for Cognitive Disorder in the Elderly (IQCODE)\textsuperscript{22} administered to a collateral informant. Participants who scored below predetermined cut points of these tests (\textless 87 on the 3MS or \textgeq 3.27 on the IQCODE; and in addition at wave 2, \textless 84 on the 3MS for those aged 80 years or older or a decline of \textgeq 3 points from the wave 1 score on the 3MS) received additional evaluation through interview of a collateral informant with the Dementia Questionnaire (DQ).\textsuperscript{23} All individuals in the high-risk 19\% stratified subsample were also investigated using the DQ interview. Participants whose 3MS and DQ results suggested cognitive difficulties, as well as all members of the 19\% subsample, then received a clinical assessment by specially trained nurses and psychometric technicians. The examination included a brief physical evaluation, a detailed history of medical and cognitive symptoms, a structured neurological examination, and a 1-hour battery of neuropsychological tests. A geriatric psychiatrist and neuropsychologist reviewed these data and assigned working diagnoses of dementia (DSM-III-R)\textsuperscript{24} or other cognitive syndromes. Participants with a working diagnosis of dementia were then invited to undergo examination by a geriatric psychiatrist and laboratory studies, including neuroimaging. To substantiate or refine their diagnoses, we re-examined these individuals 18 months after their initial evaluations. A consensus panel of experts in neurology, geriatric psychiatry, neuropsychology, and cognitive neuroscience then reviewed all available data and assigned final diagnoses. Dementia onset was defined as the year in which a participant unambiguously met DSM-III-R criteria for dementia. Diagnoses of AD followed criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA),\textsuperscript{25} while diagnoses of other dementing illnesses were also made according to current research practice.\textsuperscript{26,27} These methods have recently been shown\textsuperscript{28} to provide differential diagnoses of AD that correspond to ‘gold standard’ neuropathologic diagnoses with overall agreement of 0.76 to 0.81 and with differential diagnostic sensitivity of 0.80 to 0.93. These rates compare well with those reported previously from major referral centers and university-based clinics specializing in dementia.\textsuperscript{29,30} Using data from the fully examined 19\% subsample, we estimated that the overall sensitivity of the study’s screening and examination protocol was 93\% for detection of prevalent dementia\textsuperscript{31} and 89\% for the detection of incident dementia.\textsuperscript{32}

**STATISTICAL ANALYSES**

We compared the characteristics of AH medication users and nonusers using $t$ tests for continuous variables and $\chi^2$ tests for categorical variables. We then used discrete time survival analysis\textsuperscript{33} to examine the risk of incident AD in relation to AH medication use at baseline. We controlled for covariates shown previously in this data set to relate to the risk of AD\textsuperscript{34} and any other relevant variables found to differ among AH medication users and nonusers. The covariates included age, sex, education, and number of \textit{APOE} $\epsilon$4 alleles as well as history (yes vs no) of stroke, hypercholesterolemia (diagnosed by a physician or nurse), diabetes, and myocardial infarction. To assess whether the observed association with AH medication use was independent of blood pressure control, we examined data from the fully examined subsample in which blood pressure measurements were taken. With this data, we conducted a similar analysis that included additional parameters controlling for systolic and diastolic blood pressure. Finally, to explore whether mortality bias might explain the observed associations between AH medication use and AD, we used similar discrete time survival methods to conduct a separate analysis of the association between
AH medication use and risk of death. In these models, we examined death over the follow-up of the study as the outcome while controlling for age, sex, and education. We fit all discrete time models using SAS version 8 software (SAS Institute Inc, Cary, NC) and calculated parameter estimates with 93% profile likelihood confidence intervals. We used the conventional definition of statistical significance of P<.05 (or, alternatively, a 95% confidence interval excluding 1.0).

RESULTS

A total of 5092 elderly residents of Cache County (90% of those eligible) initially agreed to participate in the study and completed the baseline interview. Of these, 355 were found to have prevalent dementia at wave 1. A total of 3308 remaining participants completed the wave 2 procedures sufficiently to determine their cognitive status. Of these, 185 were identified as having incident dementia (104 with AD and no other dementia diagnosis). Participants with other than AD were excluded from consideration, leaving a total of 3227 for the current analysis.

A total of 1429 individuals were lost to follow-up and were not included in the current analyses. Of these, 627 (43.9%) had died, while the other 802 (56.1%) refused to complete the study, had moved out of the area, or could not be located. Compared with participants who completed the study protocol, the latter individuals were older (\( t = -5.92, P < .01 \)) and less well educated (\( t = 5.29, P < .01 \)).

Only 10 participants (<1%, 2 with AD and 8 without) in the current analysis did not provide information on AH drug use at wave 1. Among the 3217 participants who provided information, 1456 (45.3%) were using an AH medication. Among these, 419 (13.0%) were taking an ACE inhibitor, 370 (11.5%) a \( \beta \)-blocker, 480 (14.9%) a calcium channel blocker (40.0% dihydropyridine-type agents), and 851 (26.5%) a diuretic (of these, 37.8% thiazide, 35.4% potassium sparing, and 26.8% loop). Approximately 18.2% of participants were using more than 1 class of AH medication.

To assess differences between the AH medication user and nonuser groups that might be relevant to risk of AD, we compared the baseline attributes of the 2 groups (Table 1). Users of AH medications were significantly older and less educated. They were also more likely to be women and to have a history of stroke, hypercholesterolemia, diabetes, or myocardial infarction.

Table 2 shows the unadjusted and adjusted results from the discrete time survival analyses. After controlling for age, education, sex, number of \( \varepsilon 4 \) alleles at APOE, stroke, hypercholesterolemia, diabetes, and myocardial infarction, there was a significant reduction in risk of AD among baseline users of AH medications (adjusted hazard ratio [aHR], 0.64; 95% confidence interval [CI], 0.41-0.98). A similar analysis restricted to participants with a self-reported history of hypertension revealed a comparable point estimate for AH medication users vs nonusers (aHR, 0.64; 95% CI, 0.42-0.96). The observed relationship between AD and AH medications did not vary meaningfully with reported duration of use, nor were there differences across participant strata defined by sex or presence of an APOE \( \varepsilon 4 \) allele (data not shown). Further controlling for current systolic or diastolic blood pressure using data from the fully examined subsample yielded essentially similar results (aHR, 0.65; 95% CI, 0.29-1.42).

Table 1. Characteristics of Study Participants \((n = 3297)\) by Antihypertensive Medication Use in the Cache County, Utah, Study, 1995-1998

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonusers</th>
<th>AH Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1790</td>
<td>1507</td>
</tr>
<tr>
<td>Age, mean (SD), y*</td>
<td>73.4 (6.3)</td>
<td>74.9 (6.5)</td>
</tr>
<tr>
<td>Education, mean (SD), y*</td>
<td>13.5 (2.9)</td>
<td>13.2 (2.9)</td>
</tr>
<tr>
<td>Women, No. (%)*</td>
<td>975/1790 (54.5)</td>
<td>944/1507 (62.6)</td>
</tr>
<tr>
<td>History of stroke, No. (%)*</td>
<td>39/1787 (2.2)</td>
<td>101/1504 (6.7)</td>
</tr>
<tr>
<td>History of high cholesterol, No. (%)*</td>
<td>477/1770 (27.0)</td>
<td>586/1498 (39.1)</td>
</tr>
<tr>
<td>History of diabetes, No. (%)*</td>
<td>126/1786 (7.1)</td>
<td>243/1504 (16.2)</td>
</tr>
<tr>
<td>History of MI, No. (%)*</td>
<td>95/1785 (5.3)</td>
<td>272/1491 (18.2)</td>
</tr>
<tr>
<td>No. of ( \varepsilon 4 ) alleles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, No. (%)</td>
<td>1211/1776 (68.2)</td>
<td>1044/1496 (69.8)</td>
</tr>
<tr>
<td>1, No. (%)</td>
<td>524/1776 (29.5)</td>
<td>410/1496 (27.4)</td>
</tr>
<tr>
<td>2, No. (%)</td>
<td>41/1776 (2.3)</td>
<td>42/1496 (2.8)</td>
</tr>
</tbody>
</table>

Abbreviations: AH, antihypertensive; MI, myocardial infarction.

*Differences between AH medication users and nonusers were significant at \( P < .05 \).

Table 2. Prospective Association Between AH Medication Use and Incident Illness Estimated From Discrete Time Survival Analysis

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Usage</th>
<th>Alzheimer Disease, No.</th>
<th>Person-Years</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive</td>
<td>Yes</td>
<td>43</td>
<td>1413</td>
<td>0.88 (0.59-1.31)</td>
<td>0.64 (0.41-0.98)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>59</td>
<td>1702</td>
<td>5618</td>
<td>1.0</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Yes</td>
<td>15</td>
<td>404</td>
<td>1321</td>
<td>1.17 (0.65-1.96)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>87</td>
<td>2711</td>
<td>8933</td>
<td>1.0</td>
</tr>
<tr>
<td>( \beta )-Blockers</td>
<td>Yes</td>
<td>†</td>
<td>363</td>
<td>1184</td>
<td>0.56 (0.24-1.13)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>95</td>
<td>2725</td>
<td>9070</td>
<td>1.0</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Yes</td>
<td>14</td>
<td>466</td>
<td>1525</td>
<td>0.91 (0.50-1.55)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>88</td>
<td>2649</td>
<td>8729</td>
<td>1.0</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Yes</td>
<td>26</td>
<td>825</td>
<td>2712</td>
<td>0.95 (0.60-1.47)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>76</td>
<td>2290</td>
<td>7542</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin converting enzyme; AH, antihypertensive; CI, confidence interval; HR, hazard ratio.

*Adjusted hazard ratio estimated from models that control for age; sex; education; number of APOE \( \varepsilon 4 \) alleles; and history of diabetes, high levels of cholesterol, myocardial infarction, and stroke.

†Small nonzero numbers suppressed to comply with Center for Medicare & Medicaid Services privacy policy.
Analyses of different classes of AH medications suggested differences in their association with AD risk. Angiotensin converting enzyme inhibitors (aHR, 1.13; 95% CI, 0.60-1.98) and the group of calcium channel blockers (aHR, 0.86; 95% CI, 0.45-1.53) showed no suggestion of an influence on AD risk. There was a trend toward a “protective” influence of β-blockers (aHR, 0.53; 95% CI, 0.22-1.09), and use of diuretics was associated with significantly reduced risk of AD (aHR, 0.61; 95% CI, 0.37-0.98).

Stimulated by the Syst-Eur trial’s finding of protection with nitrendipine, a dihydropyridine calcium channel blocker, we further investigated differences among subclasses of calcium channel blockers (Table 3). As predicted, we found a trend toward greater risk reduction with dihydropyridine agents (aHR, 0.53; 95% CI, 0.16-1.34; vs aHR, 1.16; 95% CI, 0.55-2.20, for nondihydropyridine agents). When we examined diuretics by type, we found that all of the risk reduction associated with this class was explained by the use of potassium-sparing diuretics (aHR, 0.26; 95% CI, 0.08-0.64).

Because nearly 50% of potassium-sparing diuretic users also used another AH medication, we examined the effects of using these different agents alone and in combination in comparison with no use of any AH medication. The use of potassium-sparing diuretics alone without any other AH medication was associated with a significant reduction in AD risk (aHR, 0.09; 95% CI, 0.01-0.41). By contrast, there was little evidence of risk reduction associated with the use of another AH medication without a potassium-sparing diuretic (aHR, 0.76; 95% CI, 0.49-1.15). We repeated similar analyses separately cross-classifying the use of potassium-sparing diuretics alone and in combination with β-blockers, ACE inhibitors, and calcium channel blockers. In all cases, the most significant effect was observed specifically with potassium-sparing diuretic use, suggesting the finding with potassium-sparing diuretics was not confounded by the simultaneous use of these other medications. To further demonstrate this, we restricted the analysis to include only AH medication users and found a significant reduction in risk of AD with potassium-sparing use in comparison with use of any other AH medication (aHR, 0.24; 95% CI, 0.06-0.68).

Finally, we examined the relationship between AH medication use and mortality over the follow-up of the study to explore whether there were excess deaths among such users that might explain the observed inverse associations with AD (ie, mortality bias). Indeed, AH medication use was associated with an increased risk of death (aHR, 1.82; 95% CI, 1.53-2.17). However, use of potassium-sparing diuretics, the particular class of AH medications for which we observed the strongest inverse association with AD, was not significantly associated with excess mortality (aHR, 1.28; 95% CI, 0.91-1.79).

### Table 3. Prospective Association Between Subclasses of Calcium Channel Blockers or Diuretics and Incident Alzheimer Disease

<table>
<thead>
<tr>
<th>Drug Category Usage</th>
<th>Alzheimer Disease, No.</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blocker: dihydropyridine</td>
<td>Present: Yes † 183 597 0.66 (0.20-1.58)</td>
<td>0.53 (0.16-1.34)</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocker: nondihydropyridine</td>
<td>No: 98 2932 9657 1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Diuretics: potassium sparing</td>
<td>Yes † 315 1037 0.46 (0.16-1.01)</td>
<td>0.26 (0.08-0.64)</td>
<td></td>
</tr>
<tr>
<td>Diuretics: loop</td>
<td>No 97 2800 9217 1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Diuretics: thiazide</td>
<td>Yes † 334 1078 0.72 (0.32-1.40)</td>
<td>0.72 (0.32-1.42)</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocker: nondihydropyridine</td>
<td>Yes † 285 935 1.08 (0.53-1.99)</td>
<td>1.16 (0.55-2.20)</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocker: dihydropyridine</td>
<td>No 92 2830 9319 1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Diuretics: loop</td>
<td>Yes 16 226 768 2.33 (1.31-3.87)</td>
<td>1.45 (0.77-2.57)</td>
<td></td>
</tr>
<tr>
<td>Diuretics: thiazide</td>
<td>No 86 2889 9486 1.0</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; HR, hazard ratio.
*Adjusted hazard ratio estimated from models that control for age; sex; education; number of APOE ε4 alleles; and history of diabetes, high levels of cholesterol, myocardial infarction, and stroke.
†Small nonzero numbers suppressed to comply with Center for Medicare & Medicaid Services privacy policy.

In this large population-based study of persons aged 65 years and older, we found reduced risks of AD among participants using specific types of AH medications. Suggestive trends were observed with β-blockers and dihydropyridine calcium channel blockers. However, by far the greatest effect was seen with potassium-sparing diuretics, which were associated with more than a 70% reduction in risk of AD. A subgroup analysis in which data on measured blood pressure were available showed that controlling for blood pressure did not appreciably change the findings. Although the restricted sample size of the latter analysis limits definitive conclusions, the findings suggest that the protective effect of these AH medications may be independent of their ability to control blood pressure.

Previous studies7-18 have reported mixed findings on the association between AH medication use and cognitive function. The conflicting results may be explained in part by the different AH medications under study. Among the observational studies, the Kungsholmen Project found a significantly reduced risk of AD among AH medication users, an overwhelming majority of whom (>80%) were taking a diuretic. These results are consistent with ours, although there was no discussion of specific types of diuretics. The Swedish investigators also
found greater apparent reduction in risk among APOE ε4 carriers, but we could not replicate this finding.

Six large, randomized trials of hypertension examined the effects of AH medications on cognition. Three of these trials tested β-blockers, thiazide diuretics, or angiotensin II receptor blockers12-14 and found no collateral effect on secondary measures of cognitive performance. Two other trials tested ACE inhibitors15,16 and found some evidence for protection against cognitive difficulties associated with recurrent stroke, but the effects may have reflected an action on vascular dementia rather than AD. Only the Syst-Eur trial17,18 which tested a dihydropyridine calcium channel blocker, demonstrated a reduction in the risk of AD. Our findings therefore appear to be consistent with the results from these trials. Notably, no trial has specifically examined the cognitive effects of a potassium-sparing diuretic.

We observed the greatest reduction in AD risk specifically with potassium-sparing diuretics. It is not clear why potassium-sparing diuretics in particular should be associated with a reduced risk of AD, but it is well known that both loop and thiazide diuretics reduce plasma potassium concentration while potassium-sparing diuretics (including triamterene, spironolactone, and amiloride hydrochloride) typically lead to increased concentrations. As yet unpublished findings from the Gothenberg Study also suggest that increased potassium levels may be associated with a reduced risk of dementia.34 Consistent with this idea are observations that low potassium concentrations are associated with oxidative stress,35,36 inflammation,35,36 platelet aggregation,37 and vasocostriction,38 all of which are possible contributors to AD pathogenesis.

Among their limitations, our results can be only as precise as the accuracy of our exposure measures (in this case, AH medication use) and outcomes (the diagnosis of AD). The latter seems especially important here because of the plausible effect of AH treatment on risks of cerebrovascular disease and hence vascular dementia but not necessarily AD. In fact, a recent study39 suggested that participants in population-based studies may be misdiagnosed with AD when considerable cerebrovascular pathology is undetected. However, we doubt that this sort of misclassification explains our findings. Our diagnoses adhered to conventional diagnostic criteria, and our AD diagnoses have been shown to have accuracy similar to that obtained in specialty dementia clinics. We also note that MRI scans were available for 56% of our AD cases, and in each instance these scans failed to reveal vascular pathology sufficient to deter a diagnosis of uncomplicated AD.

As is true in all observational studies, our results may also be vulnerable to confounding, ie, to the possibility that the relation of AH medication use and AD risk reflects the association of both to another variable. Some confounding variables may be measured and controlled. For instance, we found that AH medication users were older, less well educated, more likely to be women, and more likely to have greater burden of vascularopathy. All of these variables, which are typically associated with increased risk of AD, could spuriously lead to a higher risk of AD observed among AH users. Statistical adjustment for these variables produced the result that AH medication use was, in fact, associated with a decreased risk of AD. By contrast, other sources of confounding may be unmeasured and therefore uncontrolled. For example, confounding by indication could produce a spurious association between AH medications and AD, which really reflects a clinical indication for treatment. We could not control for indication in these analyses because people take AH medications almost exclusively to control hypertension; thus, we could not separate (or measure) the indication apart from the treatment. We do note, however, that a growing body of evidence suggests that hypertension, at least in middle life, is a risk factor for AD and that this sort of confounding would therefore be expected to bias results toward an increased apparent risk of AD among AH users, ie, the opposite of what we observed. It is, of course, possible that unrecognized and/or untreated hypertension could elevate the risk of AD among nonusers of AH medications. This possibility could then explain a reduced apparent risk among the users of AH medications. However, it cannot explain the analysis restricted to AH medication users in which risk was reduced specifically with potassium-sparing diuretics.

Another potential limitation is mortality bias. Users of AH medications who developed incident AD might have been more likely than nonusers to die during the interval between wave 1 and wave 2 and therefore to have escaped detection. This would in turn lead to an apparent inverse association between AH use and AD risk. Indeed, we found that AH medication use was associated with increased mortality over the study period. But we did not observe any evidence for increased mortality with use of potassium-sparing agents, which showed the strongest relationship with risk of AD.

Finally, it is possible that our findings with AH medications may have occurred by chance. We examined several subclasses of AH medications but did not correct for multiple comparisons. We chose not to do so for 2 reasons. First, the hypothesis that AH medications may protect against AD is supported by prior evidence from several previous studies that have observed similar effects. Second, the usual forms of correction for multiple comparisons lead to high risk of a so-called type II error in which real findings are ignored. We prefer to state the findings here with the caveat that the effects with specific subclasses, primarily potassium-sparing diuretics, will require replication in new data.

Our study also has several notable strengths. Its sample was sufficiently large to enable examination of different subclasses of AH medications while controlling for important potential influences such as age, sex, APOE genotype, and some forms of vascular comorbidity. Because we studied an entire population rather than a population-based or convenience sample, there is reduced threat of selection bias. This same threat was presumably mitigated further by the unusually high response rates of the Cache County residents.

In sum, our findings suggest that AH medications may reduce the risk of AD and that potassium-sparing diuretics and possibly dihydropyridine-type calcium channel blockers or β-blockers may have particular benefit. We suggest these findings should prompt further epidemiolog-
logic and basic science studies into the possible neuroprotective effects of these drugs.

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