Diuretic use is associated with better learning and memory in older adults in the Ginkgo Evaluation of Memory study

Sevil Yasar, Fu-Mei Lin, Linda P. Fried, Claudia H. Kawas, Kaycee M. Sink, Steven T. DeKosky, Michelle C. Carlson, for the Ginkgo Evaluation of Memory (GEM) Study Investigators

Abstract

Background: To investigate the association between diuretics, angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (AT2RB), and cognitive function.

Methods: This post hoc analysis of the randomized controlled Ginkgo Evaluation of Memory Study trial focuses on 3069 nondemented community-dwelling participants aged >75 years. At baseline visit, detailed information about medication use was collected and five cognitive domains were assessed. Multivariate linear regression analyses were used to assess cross-sectional associations between medication use and cognitive function.

Results: In all, 36% of participants reported history of hypertension and 53% reported antihypertensive medication use, with 17% reporting diuretic, 11% ACE-I, and 2% AT2RB use. Potassium-sparing diuretic use (N = 192) was associated with better verbal learning and memory measured by California Verbal Learning Test as compared with no antihypertensive medication users (β = 0.068, P = .01; β = 0.094, P < .001) and other antihypertensive medication users (β = 0.080, P = .03; β = 0.153, P < .001). Use of ACE-I or AT2RB was not associated with better cognitive function.

Conclusion: Results warrant further investigation into possible protective effects of potassium-sparing diuretics and the role of potassium in mitigating cognitive decline.

Keywords: Cognitive function; Diuretic; Angiotensin-converting enzyme inhibitor; Angiotensin receptor blocker

1. Introduction

There is increasing awareness of a possible role of the brain renin-angiotensin system (RAS) in cognitive function and Alzheimer’s disease (AD). In animal studies, continuous activation of the RAS through the angiotensin II type 1 receptor is associated with decreased cerebral blood flow and increased oxidative stress that may impair cognitive function [1]. Numerous randomized clinical trials have evaluated effects of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (AT2RB), which act on the RAS and on cognitive function in hypertensive patients, giving mixed results [2–9]. Additionally, studies found no protective effect on cognitive decline of ACE-I, AT2RB, and combined ACE-I and AT2RB use in participants with cardiovascular disease or diabetes [10] and of AT2RB use in participants with recent ischemic stroke [11]. Most studies of these medications are confounded by combined use with beta blockers, diuretics, or each other. Additionally, they were unable to specify the type of antihypertensive medications, and cognitive function
was often a secondary endpoint, measured by instruments designed to screen for cognitive impairment. However, one small clinical trial found that use of blood-brain barrier crossing (BBBC) ACE-Is decreased the rate of global cognitive decline in subjects with AD [12]. In our recent study, diuretic and ACE-I use for >3 years was associated with reduced incidence of impairments in memory and executive function [13].

On the basis of these findings, we hypothesized that use of diuretics, ACE-Is, or AT2RBs would be associated with better performance in memory and possibly other domains of cognitive function. In a large national study, the Ginkgo Evaluation of Memory Study (GEMS) [14], we examined whether the reported use of diuretics, ACE-I, or AT2RB was associated with better function in domains beyond global cognition, including psychomotor speed, executive function, verbal learning and memory, and visuospatial function, in nondemented community-dwelling participants aged ≥75 years.

2. Methods

2.1. Participants and study design

This study is a post hoc analysis of baseline cognitive data of the randomized controlled GEMS trial. The GEMS is a double-blind, randomized, controlled clinical trial of 3072 nondemented individuals aged ≥75 years to assess *Ginkgo biloba* 240 mg/d versus placebo for the prevention of dementia over a period of 6.1 years. This trial was conducted under an investigational new drug application with the Food and Drug Administration under the auspices of National Center of Complementary and Alternative Medicine and registered at clinicaltrials.gov (Trial Registration Identifier: NCT00010803). Details and results of the study have been published previously [14–16]. Because of ineligibility, three participants were later excluded after randomization, leaving 3069 cognitively intact participants aged between 75 and 96 years. Participants were recruited from four communities in the United States: Hagerstown, MD; Pittsburgh, PA; Winston-Salem/Greensboro, NC; and Sacramento, CA. At each stage of the recruitment process, cognitive, medical, and other exclusion criteria were applied [14].

Screening visits included the Modified Mini-Mental State Examination (3MS) [17] and participants with a score of ≥80 were allowed to progress to a more rigorous battery of 14 neuropsychological tests [14]. Participants were eligible for entry into the GEMS if they achieved passing scores on all or all but one cognitive domain and met all other criteria [14], which allowed participants with normal cognition or mild cognitive impairment to be enrolled in the study. Demographic and baseline health characteristics were assessed using questionnaires, and included age, race, gender, and years of education. Anthropometric measures included height and weight. Co-morbidities, including depressive symptoms, were ascer-

tained and measured by the Center for Epidemiologic Studies Depression Scale [18], and medical history was based on self-report of a history of 16 diseases, including myocardial infarction, angina, stroke, transient ischemic attack (TIA), heart failure, hypertension (HTN), diabetes mellitus (DM), and atrial fibrillation.

2.2. Exposure assessment

Detailed information about medication use was collected at each visit by asking participants to bring in all prescribed medications, prescriptions, and over-the-counter medications. All available medication vials were visually inspected. Data regarding names, dosages, frequency of prescription, frequency of medication actually taken in the past 2 weeks, and routes of administration were recorded and 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, chlorothalidine, chlorothiazide, ethacrynic acid, furosemide, hydrochlorothiazide, indapamide, metolazone, methylchlorothiazide, spironolactone, torsemide, triamterene), ACE-I (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril), or AT2RB (candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan). Diuretics were further divided into those that were potassium-sparing ([Ksparing] bumetanide, chlorothalidine, chlorothiazide, ethacrylic acid, furosemide, hydrochlorothiazide, indapamide, metolazone, methylchlorothiazide, torsemide), and those that were nonpotassium-sparing ([Knsparing] bumetanide, chlorothalidine, chlorothiazide, ethacrylic acid, furosemide, hydrochlorothiazide, indapamide, metolazone, methylchlorothiazide, torsemide), based on previous findings that only Ksparing diuretics decreased the incidence of AD [19,20]. In addition, diuretics were also divided into thiazide diuretics (amiloride, chlorothalidone, chlorothiazide, hydrochlorothiazide, metolazone, methylchlorothiazide, spironolactone, triamterene), which are effective antihypertensive agents, and loop diuretics (bumetanide, furosemide, torsemide, ethacrynic acid), which are more often used for diuresis. ACE-Is were further divided into those that cross the blood-brain barrier (BBBC) (captopril, fosinopril, lisinopril, perindopril, ramipril, trandolapril) and those that do not cross the blood-brain barrier (BBBNC) (benazepril, enalapril, moexipril, quinapril). This classification was used to address previous findings that use of BBBC ACE-I decreased the rate of cognitive decline in mild to moderate AD and in initially cognitively normal participants [12,21]. Classification was primarily based on reviews of the literature and medication package inserts.

2.3. Outcome measures

The baseline cognitive test battery was designed to comprehensively assess major domains of cognitive function in healthy older adults, and to be maximally sensitive to normal age-related changes in cognition and to pathological changes.
associated with incident dementia [22,23]. Five major cognitive domains were assessed, which included attention and psychomotor speed; verbal and visual memory; language function; visuospatial, constructional function; and executive function. Cut-off scores for impairment were derived from the Cardiovascular Health Study (CHS) cognition study [24,25]. In the present study, we assessed the associations of medications and global cognitive status (3MS), verbal learning and memory (California Verbal Learning Test-short delayed free recall [CVLT-FRS], CVLT-long delayed free recall [FRL] [26], and CVLT-sum of trials [CVLT-Sum] 1 to 5 of List A), visuospatial construction (Modified Rey-Osterrieth Complex Figure Test copy [RO-Copy] [27]), visual learning and memory (RO-immediate recall [RO-IR] and RO-delayed recall [RO-DR] [27]), attention and psychomotor speed (Trail Making Test Part A [TMT-A] [28]), and executive function (Trail Making Test Part B [TMT-B] [28]).

2.4. Statistical analyses

The main objective was to estimate the associations between diuretic, ACE-I, and AT2RB use and baseline cognitive functions. Of the 3069 nondemented participants at baseline, 362 (11%) were excluded because they reported concurrent use of ACE-I and diuretics (N = 179), or ACE-I and AT2RBs (N = 1), or diuretics and AT2RBs (N = 53), or beta blockers and diuretics (N = 101), or vasodilators and diuretics (N = 28), resulting in a final sample of 2707 participants for comparative analyses. Of these, 1318 reported no use of antihypertensive medications, 560 reported use of other types of antihypertensive medications (calcium channel blockers, β-receptor blockers, vasodilators), 459 reported diuretic use only, 309 reported ACE-I use only, and 61 reported AT2RB use only. The 362 participants who were not included did not differ in demographic or cognitive characteristics from the study sample.

We compared baseline characteristics of diuretic, ACE-I, and AT2RB users with nondrug (C) and other types of antihypertensive drug (O)-treated participants using comparisons between groups for outcomes by analysis of variance or Chi-square test.

Multivariate linear regression analyses were used to evaluate the association between cognition across domains and antihypertensive medication use by using SAS version 9.1. (SAS Institute Inc., Cary, NC), and unstandardized regression coefficients were reported. The results were considered significant if P < .05 in two-tailed comparisons.

To assess the possible associations between specific antihypertensive medications (diuretic, ACE-I, or AT2RB), we used other antihypertensive drug-treated group as one control group, and to assess the possible role of HTN and its treatment, we used nondrug treated-group as another control group. The other antihypertensive drug group included participants reporting use of calcium channel blockers, beta blockers, or vasodilators and at the same time did not report use of diuretic, ACE-I, or AT2RB. First, we evaluated the associations between diuretics and cognitive function as compared with the two different control groups. Then, in separate analyses, we stratified diuretic use according to use of loop or thiazide diuretics and according to the use of Ksparing and KNsparing diuretics. Similar analyses were carried out to evaluate the associations between ACE-I and AT2RB use on cognitive functions as compared with the two different control groups. Analyses were then stratified according to the use of BBBC and BBBNCE ACE-I.

Analyses were adjusted for the potential confounding effects of age, gender, race (categorized as white vs nonwhite), education (categorized as <12, 12, >12 years of education), income (categorized as <$36,000/yr, $36,000–52,500/yr, >$52,500/yr), and health-related behaviors, including smoking status (never, former, current) and alcohol consumption (per week: never, former, <1 drink/wk, ≥1 drink/wk, ≥1 drink/d, and ≥2 drink/d). Analyses were also individually adjusted for comorbidities, such as history of HTN, stroke (cerebrovascular accident [CVA]) or TIA, DM, congestive heart failure (CHF), coronary artery disease (CAD), renal disease (measured by serum creatinine, mg/dL), depression (measured by using Center for Epidemiologic Studies Depression Scale), body mass index (kg/m²), and mean systolic blood pressure (SBP, mm Hg) and diastolic blood pressure (mm Hg).

3. Results

3.1. Participants

The mean age of the 2707 participants was 78.6 years, among which 55% were male, 96% were white, and 64% had college education. A total of 36% reported HTN, and mean systolic (SD) and diastolic blood pressures were 135.32 (3.89) and 69.09 (0.9) mm Hg, respectively. The prevalence of DM, CAD, CHF, and CVA was 8%, 18%, 1%, and 3%, respectively (Table 1). The baseline means (SD) 3MS, CVLT-FRS and FRL scores, and TMT-A and TMT-B periods (seconds) were indicative of a high functioning sample (Table 2).

Of the 2707 participants included in the analyses, 53% reported antihypertensive medication use. Specifically, 17% reported diuretic, 11% ACE-I, 2% AT2RB, and 21% other antihypertensive medication use. Diuretic and AT2RB users were predominantly women, whereas ACE-I and other antihypertensive drug users were predominantly men. Diuretic, ACE-I, AT2RB, and other antihypertensive drug users had a higher prevalence of HTN, CAD, TIA, and CVA, whereas ACE-I and diuretic users had a higher prevalence of CHF and impaired renal function, and ACE-I and AT2RB had higher prevalence of DM, when compared with the nondrug group. All antihypertensive medication users, including other antihypertensive drug, diuretic, ACE-I, and AT2RB users, had higher SBP as compared with the nondrug group (Table 1). There were no significant differences in baseline...
Table 1
Demographics and baseline characteristics of study participants

| Characteristics | Overall | Nondrug group (C) | Other antihypertensive drug group (O) | ACE-I users | Diuretic users | AT2RB Users | \( P \) |
|-----------------|---------|-------------------|--------------------------------------|-------------|---------------|-------------|--------|
| N               | 2707    | 1318 (48)         | 560 (21)                             | 309 (11)    | 459 (17)      | 61 (2)      | .494   |
| Age, mean (SD)  | 78.5 ± 3.3 | 78.7 ± 3.3       | 78.6 ± 3.1                           | 78.8 ± 3.4  | 78.6 ± 3.5    | .990        | .990   |
| Gender          | Male    | 1476 (55)         | 380 (68)                             | 196 (63)    | 182 (40)      | 30 (49)     | .000   |
| Race            | White   | 2593 (96)         | 531 (95)                             | 296 (96)    | 430 (94)      | 58 (95)     | .027   |
| Education       | <12 years | 293 (11)          | 53 (9)                               | 34 (11)     | 61 (13)       | 10 (16)     | .000   |
|                | ≥12 years | 1743 (64)        | 366 (65)                             | 192 (62)    | 283 (62)      | 28 (46)     | .063   |
| Income          | 36,000  | 706 (26)          | 148 (26)                             | 89 (29)     | 125 (27)      | 15 (25)     | .76    |
|                | 36,000–52,000 | 1332 (49)     | 269 (48)                             | 135 (44)    | 245 (53)      | 35 (57)     | .133   |
| Smoking         | Never   | 1080 (41)         | 208 (37)                             | 109 (35)    | 204 (44)      | 10 (16)     | .43    |
|                | Former  | 1456 (54)         | 320 (57)                             | 227 (49)    | 38 (2)        | 16 (2)      | .000   |
|                | Current | 121 (5)           | 22 (4)                               | 19 (6)      | 17 (4)        | 0 (0)       | .000   |
| Hx HTN          | 984 (36)| 307 (55)          | 238 (77)                             | 329 (72)    | 53 (87)       | .000        | .000   |
| Hx DM           | 216 (8) | 40 (7)            | 76 (25)                              | 33 (7)      | 10 (16)       | .000        | .000   |
| Hx CAD          | 481 (18)| 180 (32)          | 76 (25)                              | 92 (20)     | 17 (28)       | .000        | .000   |
| Hx CVA          | 77 (3)  | 15 (2)            | 17 (6)                               | 19 (4)      | 2 (3)         | .003        | .000   |
| Hx TIA          | 189 (7) | 55 (10)           | 32 (10)                              | 43 (9)      | 9 (15)        | .000        | .000   |
| Hx CHF          | 37 (1)  | 9 (2)             | 12 (4)                               | 9 (2)       | 0 (0)         | .000        | .000   |
| Hx AF           | 207 (8) | 72 (13)           | 34 (11)                              | 30 (7)      | 6 (10)        | .000        | .000   |
| BMI mean (SD)   | 26.9 ± 4.2 | 26.2 ± 4.0       | 27.1 ± 3.9                           | 27.1 ± 4.1  | 28.3 ± 4.5    | 28.6 ± 4.4  | .000   |
| SBP mean (SD)   | 132.9 ± 18.2 | 130.6 ± 17.2   | 135.1 ± 18.9                         | 135.2 ± 19.9| 134.3 ± 17.4 | 141.4 ± 20.7| .000   |
| DBP, mean (SD)  | 69.0 ± 9.8 | 69.1 ± 10.1      | 67.8 ± 10.9                          | 68.8 ± 9.9  | 70.3 ± 10.5   | .195        | .000   |
| Serum creatinine, mean (SD) | 0.98 ± 0.23 | 0.94 ± 0.2    | 1.00 ± 0.23                          | 1.05 ± 0.26 | 1.04 ± 0.26   | 0.98 ± 0.23  | .000   |

Abbreviations: Hx, history; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease including heart attack, angina, and coronary bypass surgery; CVA, cerebrovascular disease; TIA, transient ischemic attack; CHF, congestive heart failure; AF, atrial fibrillation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE-I, angiotensin-converting enzyme inhibitor; AT2RB, angiotensin II receptor blocker.

Values listed are N% or mean ± SD.

\( P \) values are comparisons across 5 groups by analysis of variance or Chi-square test.

There were no significant differences in baseline cognitive functions between control groups and ACE-I and AT2RB (Table 2).

3.2. Diuretic, ACE-I, and AT2RB use and cognitive function

In multivariate regression analyses, we found that other antihypertensive drug and nondrug group did not differ in following cognitive functions assessed in this study: 3MS, TMT-A, TMT-B, CVLT-FSR, CVLT-FLR, CVLT-Sum, RO-IR, RO-DR, RO-Copy (3MS: \( \beta = -0.007, SE = 0.25, P = .76 \); TMT-A: \( \beta = -0.007, SE = 0.87, P = .77 \); TMT-B: \( \beta = -0.035, SE = 2.3, P = .13 \); CVLT-FSR: \( \beta = -0.005, SE = 0.17, P = .82 \); CVLT-FLR: \( \beta = -0.019, SE = 0.17, P = .43 \); CVLT-Sum: \( \beta = -0.020, SE = 0.54, P = .40 \); RO-IR: \( \beta = -0.033, SE = 0.23, P = .18 \); RO-DR: \( \beta = -0.014, SE = 0.23, P = .57 \); RO-COPY: \( \beta = -0.017, SE = 0.15, P = .48 \).

Diuretic use was associated with better verbal learning and memory (CVLT-FRS, CVLT-FRL, and CVLT-Sum) when compared with nondrug group (\( \beta = 0.048, SE = 0.18, P = .05 \); \( \beta = 0.048, SE = 0.18, P = .05 \); \( \beta = 0.057, SE = 0.57, P = .02 \), respectively) and other antihypertensive drug group (\( \beta = 0.053, SE = 0.21, P = .1 ; \beta = 0.076, SE = 0.21, P = .02 ; \beta = 0.104, SE = 0.64, P < .001 \), respectively) (Table 3). Further, the diuretic use was classified according to the use of loop or thiazide diuretics and no association was found between loop or thiazide diuretics and cognitive functions. However, when diuretics were stratified according to the use of Ksparing and KNsparing, it was found that Ksparing diuretics were responsible for the better performance on verbal learning and memory (CVLT-FRS, CVLT-FRL, and CVLT-Sum) when compared with the nondrug group (\( \beta = 0.068, SE = 0.25, P = .01 \); \( \beta = 0.094, SE = .000 \).
Table 2
Baseline cognitive characteristics of study participants

| Cognitive tests | Overall | Non-drug group (C) | Other antihypertensive drug group (O) | ACE-I users | Diuretic users | AT2RB users |
|-----------------|---------|-------------------|--------------------------------------|-------------|---------------|-------------|
| 3MS             | 93.4 ± 4.7 | 93.6 ± 4.7        | 93.1 ± 4.7                           | 93.4 ± 4.6  | 92.4 ± 4.8    |             |
| TMT-A           | 43.7 ± 16.3 | 43.3 ± 16.1       | 44.0 ± 16.2                          | 43.7 ± 14.5 | 44.6 ± 18.1  | 43.4 ± 17.2 |
| TMT-B           | 110.7 ± 45.2 | 107.2 ± 43.8      | 113.5 ± 46.4                         | 111 ± 42.4  | 116.6 ± 47.8 | 113.7 ± 50.1|
| CVLT-FRS        | 8.1 ± 3.2  | 8.2 ± 3.2         | 7.7 ± 3.2                            | 7.9 ± 3.0   | 8.3 ± 3.1    | 8.2 ± 3.1   |
| CVLT-FRL        | 8.8 ± 3.2  | 8.9 ± 3.3         | 8.4 ± 3.2                            | 8.7 ± 3.3   | 9.2 ± 3.0    | 9.2 ± 2.9   |
| CVLT-Sum        | 43.3 ± 10.5 | 43.7 ± 10.8       | 41.6 ± 10.1                          | 42.2 ± 10.3 | 44.9 ± 9.7   | 43.6 ± 10.7 |
| RO-IR           | 14.7 ± 4.3 | 14.9 ± 4.3        | 14.6 ± 4.1                           | 14.6 ± 4.2  | 14.3 ± 4.2   | 14.2 ± 4.1  |
| RO-DR           | 13.8 ± 4.3 | 14.0 ± 4.4        | 13.8 ± 4.1                           | 13.8 ± 4.3  | 13.3 ± 4.2   | 13.7 ± 4.2  |
| RO-Copy         | 20.0 ± 2.8 | 20.0 ± 2.8        | 20.0 ± 2.7                           | 19.9 ± 2.8  | 20 ± 2.9     | 19.7 ± 2.5  |

Abbreviations: 3MS, Modified Mini-Mental State Examination; TMT-A, trail making test, part A; TMT-B, trail making test, part B; CVLT, California Verbal Learning Test; CVLT-FRS, CVLT short delayed free recall; CVLT-FRL, CVLT long delayed free recall; CVLT-Sum, CVLT sum of trials (1 to 5 of List A); RO, Rey-Osterrieth complex figure test (RO-IR, immediate recall; RO-DR, delayed recall; RO-Copy, copy).

Values listed are mean ± SD.

0.25, P < .001; β = 0.067, SE = 0.81, P = .01, respectively) and other antihypertensive drug group (β = 0.080, SE = 0.28, P = .03; β = 0.153, SE = 0.28, P < .001; β = 0.126, SE = 0.85, P < .001, respectively) (Table 3).

In contrast, no differences were found in any of the six cognitive outcomes between those receiving either ACE-Is and AT2RBs and those not receiving when compared with non-drug or other antihypertensive drug group (Table 4). Stratification of ACE-Is according to blood-brain barrier permeability was not associated with better cognitive function (Table 4).

4. Discussion

In this cross-sectional study of nondemented, community-dwelling older participants of the GEMS clinical trial, we evaluated associations between use of diuretics, ACE-I, and AT2RB on key domains of cognition, including psychomotor speed, executive function, verbal learning and memory, and visuospatial function. We demonstrated that Ksparing diuretic use was selectively associated with better performance on verbal learning and memory, as compared with other and no antihypertensive medication users. Although observed associations were modest, they were highly significant and selective.

Numerous clinical trials have assessed antihypertensive medications and their effects on cognitive function with mixed results. Some clinical trials showed protective effects of diuretics [2] and ACE-Is [3,29], whereas others showed no effect of ACE-Is [2,4,10,30], thiazide diuretics [4,31,32], or AT2RBs [7,10,11]. These studies had two key weaknesses. First, they were unable to specify the type of antihypertensive medications. Second, cognitive function was often a secondary endpoint, measured by using blunt instruments designed to screen for cognitive impairment. In this study, we extended our previous work in community-dwelling older individuals, where we observed that diuretic and ACE-I use for more than 3 years was selectively associated with reduced incidence of impairment in memory and executive function [13]. Other prospective studies also suggested protective effects of Ksparing

| Medications | N | β     | SE  | β     | SE  | β     | SE  | β     | SE  | β     | SE  | β     | SE  | β     | SE  |
|-------------|---|-------|-----|-------|-----|-------|-----|-------|-----|-------|-----|-------|-----|-------|-----|
| Diuretic vs C | 459 | 0.028 | 0.26 | 0.017 | 0.98 | 0.043 | 2.51 | 0.048* | 0.18 | 0.048* | 0.18 | 0.057* | 0.57 | 0.002 | 0.25 | 0.019 |
| Diuretic vs O | 0.26 | 0.30 | 0.021 | 1.17 | 0.036 | 3.09 | 0.053 | 0.21 | 0.076* | 0.21 | 0.104* | 0.64 | 0.021 | 0.28 | 0.013 |
| Loop vs C | 111 | 0.052 | 0.50 | 0.007 | 1.81 | 0.046 | 4.62 | 0.002 | 0.34 | 0.030 | 0.34 | 0.002 | 1.10 | 0.028 | 0.47 | 0.051 |
| Loop vs O | 0.076 | 0.53 | 0.021 | 1.94 | 0.047 | 5.17 | 0.012 | 0.36 | 0.026 | 0.36 | 0.026 | 1.11 | 0.036 | 0.47 | 0.078* |
| Thiazide vs C | 165 | 0.023 | 0.38 | 0.018 | 1.40 | 0.046 | 3.59 | 0.017 | 0.26 | 0.046 | 0.28 | 0.84 | 0.002 | 0.36 | 0.015 |
| Thiazide vs O | 0.019 | 0.42 | 0.032 | 1.59 | 0.051 | 4.24 | 0.021 | 0.28 | 0.011 | 0.29 | 0.065 | 0.89 | 0.019 | 0.39 | 0.019 |
| Ksparing vs C | 192 | 0.041 | 0.36 | 0.015 | 1.30 | 0.014 | 3.43 | 0.068* | 0.25 | 0.094* | 0.25 | 0.067* | 0.81 | 0.006 | 0.35 | 0.004 |
| Ksparing vs O | 0.049 | 0.40 | 0.007 | 1.44 | 0.004 | 4.05 | 0.080* | 0.28 | 0.153* | 0.28 | 0.126* | 0.85 | 0.024 | 0.36 | 0.015 |
| KNsparing vs C | 267 | 0.001 | 0.32 | 0.013 | 1.21 | 0.054* | 3.01 | 0.010 | 0.22 | 0.017 | 0.22 | 0.023 | 0.71 | 0.010 | 0.31 | 0.034 |
| KNsparing vs O | 0.011 | 0.36 | 0.032 | 1.41 | 0.057 | 3.62 | 0.011 | 0.24 | 0.006 | 0.046 | 0.33 | 0.017 | 0.22 |

Abbreviations: β, beta coefficient; SE, standard error; C, no antihypertensive medication use; O, other antihypertensive medication use (calcium channel blockers, beta blockers, others).

*P < .05,
†P < .01,
‡P < .001.
Table 4
Cross-sectional multivariate linear regression association of cognitive function between ACE-I and AT2RB users compared with no antihypertensive medication or other antihypertensive medication users

| Medication | 3MS   | TMT-A | TMT-B | CVLT-FRS | CVLT-FRL | CVLT-Sum | RO-IR | RO-DR | RO-Copy |
|------------|-------|-------|-------|----------|----------|----------|-------|-------|---------|
| ACE-I vs C | β     | β     | β     | β        | β        | β        | β     | β     | β       |
| 0.014     | 0.31  | -0.007| 2.9   | 0.018    | 0.21     | 0.011    | 0.21  | 0.001 | 0.69    |
| ACE-I vs O | β     | β     | β     | β        | β        | β        | β     | β     | β       |
| -0.020    | -0.099| -0.025| 3.2   | 0.029    | 0.23     | 0.034    | 0.23  | 0.009 | 0.72    |
| ACE-I BBBC vs C | β     | β     | β     | β        | β        | β        | β     | β     | β       |
| -0.007    | 0.36  | 0.011 | 3.3   | 0.004    | 0.25     | -0.011  | 0.81  | -0.028| 0.35    |
| ACE-I BBBC vs O | β     | β     | β     | β        | β        | β        | β     | β     | β       |
| 0.011     | 0.38  | 0.023 | 3.7   | 0.009    | 0.26     | 0.021    | 0.27  | -0.010| 0.82    |
| ACE-I BBBCN vs C | β     | β     | β     | β        | β        | β        | β     | β     | β       |
| -0.015    | -0.008| -0.004| 4.5   | 0.031    | 0.33     | 0.016    | 0.33  | 0.022 | 1.1     |
| ACE-I BBBCN vs O | β     | β     | β     | β        | β        | β        | β     | β     | β       |
| -0.026    | -0.016| -0.019| 5.0   | 0.039    | 0.35     | 0.038    | 0.35  | 0.034 | 1.1     |
| AT2RB vs C | β     | β     | β     | β        | β        | β        | β     | β     | β       |
| -0.027    | 0.009 | -0.001| 5.7   | 0.026    | 0.42     | 0.028    | 0.42  | 0.016 | 1.4     |
| AT2RB vs O | β     | β     | β     | β        | β        | β        | β     | β     | β       |
| -0.063    | 0.64  | -0.020| 2.3   | -0.014   | 6.3      | 0.024    | 0.43  | 0.016 | 1.4     |

Abbreviations: BBBC, blood-brain barrier crossing; BBBNC, blood-brain barrier noncrossing.

The reported use of ACE-Is and AT2RBs was not associated with better cognitive functions, confirming the previous negative findings in randomized controlled clinical trials [2,4,5,7,9–11]. However, these results are in contrast with our recent prospective study in which ACE-I use for >3 years was associated with a reduced incidence of cognitive impairment [13] and another study, in which centrally acting ACE-Is slowed the decline of global cognitive function [21]. These conflicting results could be explained by the fact that positive associations in both studies were observed for cumulative use of ACE-Is, which we were not able to capture in this cross-sectional study, and the same could be true for AT2RBs. Additionally, the small number of AT2RB users may have limited our ability to detect a significant association and increased the likelihood of type II error.

There are several advantages of this study. First, our study included a large, well characterized cohort of volunteers who were extensively screened to be free of baseline dementia by using an extensive battery of cognitive and clinical measures. Second, medication use was visually validated. Third, we had sufficient power to separate diuretic and ACE-I users by excluding those who reported concomitant use of any of these medications. Nonetheless, we cannot account for the effect of past blood pressure levels, such as severity and length, and for medication use because we did not know what the participants were taking before this study. The strength of exclusion of multiple antihypertensive medication users from our analysis may at the same time be a weakness because multiple antihypertensive medication users may have represented a more difficult-to-control hypertensive group, and this should be eluded in future studies. Fourth, we were able to use two control groups (no antihypertensive medication users, allowing us to assess drug-specific effects. Additionally, our study population was highly educated and homogenous with respect to race, limiting its generalizability. Although medications were visually inspected during visits, we could not accurately determine compliance and did not have information on previous use of these medications. Similar to 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 CAD, all of which are implicated in cognitive diuretics on the development of AD [20] and on global cognitive decline in subjects with AD [19].

In this study, use of Ksparing diuretics was associated with better verbal learning and memory, when compared with no antihypertensive medication users, but also when compared with other antihypertensive medication users. The two control groups had either similar (other antihypertensive medication group) or lower (no antihypertensive medication group) SBP than the diuretic users, which suggest a drug-specific effect rather than an effect resulting from blood pressure lowering. There was no difference between thiazide or loop diuretic users, suggesting that the observed protective associations of Ksparing diuretics may have resulted from increased potassium levels. Potassium lowers blood pressure [33] through a vasodilator effect [34,35]; however, there is also evidence that potassium may be lowering blood pressure by decreasing oxidative stress or inflammation [36,37], both of which may accelerate mechanisms involved in neurodegenerative diseases, such as AD [38,39] and other age-related diseases [40,41]. One prospective study showed a positive relationship between low midlife serum potassium levels and low late-life cerebrospinal fluid levels of amyloid-beta (Aβ42), a hallmark for AD that was independent of blood pressure [42]. These findings in conjunction with the findings of present study in nondemented older adults suggest involvement of low serum potassium levels in the neurodegenerative process of AD. One weakness of the present study is that serum potassium level was unavailable, as a result of which its possible association with cognitive functions could not be evaluated. Our findings could also be because of the fact that more women were using diuretics. However, because 60% of Ksparing and also 60% of KNsparing diuretic users were women, gender cannot explain the positive associations on learning and memory of Ksparing diuretics.

The strength of exclusion of multiple antihypertensive medication users from our analysis may at the same time be a weakness because multiple antihypertensive medication users may have represented a more difficult-to-control hypertensive group, and this should be eluded in future studies. Fourth, we were able to use two control groups (no antihypertensive medication users, and other antihypertensive medication users), allowing us to assess drug-specific effects. Additionally, our study population was highly educated and homogenous with respect to race, limiting its generalizability. Although medications were visually inspected during visits, we could not accurately determine compliance and did not have information on previous use of these medications. Similar to 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 CAD, all of which are implicated in cognitive impairment.

Abbreviations: BBBC, blood-brain barrier crossing; BBBNC, blood-brain barrier noncrossing.
impairment and are main indications for use of diuretics, ACE-Is, and AT2RBs. Additionally, in a separate analysis, we included only those participants with a history of HTN (N = 1098) and who were able to replicate our findings in the Ksparing diuretic user group when compared with non-drug group (CVLT-FRS: $\beta = 0.21$, $P = .09$; CVLT-FRL: $\beta = 0.159$, $P = .025$; CVLT-Sum: $\beta = 0.160$, $P = .02$) and other antihypertensive drug group (CVLT-FRS: $\beta = 0.071$, $P = .09$; CVLT-FRL: $\beta = 0.155$, $P < .001$; CVLT-Sum: $\beta = 0.102$, $P = .01$). Another potential limitation is survival bias because users of antihypertensive medications might be more likely to die as a result of increased mortality risk associated with HTN; however, this was addressed by using a control group of nondrug users which had significantly lower blood pressures as compared with all other groups. Additionally, because there is a large cost difference between Ksparing diuretics and AT2RBs as compared with KNSparing diuretics and ACE-Is, we cannot rule out substantial residual confounding by socioeconomic status as our categories were based on income only.

In summary, this cross-sectional study found that use of Ksparing diuretic was associated with better verbal learning and memory in nondemented older individuals, suggesting a neuroprotective effect. The consistent and selective pattern of association between Ksparing diuretic use and memory warrants further longitudinal investigations to evaluate possible protective effects of Ksparing diuretics and the role of potassium in normal aging. Further investigations should also focus on how these modest differences among healthy older adults in verbal learning and memory may translate to patients using Ksparing diuretics, so as to determine clinical relevance. Longitudinal studies are also needed to determine whether Ksparing diuretic use is associated with mitigation of cognitive decline over time. This could lead to improved identification of pharmacologic targets for preventive interventions to slow cognitive decline and possibly delay progression to dementia.

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GEM Study Personnel: Project Office: Richard L. Nahin, PhD, MPH, Barbara C. Sorkin, PhD, National Center for Complementary and Alternative Medicine. Clinical Centers: Michelle Carlson, PhD, Linda Fried, MD, MPH, Pat Crowley, MS, Claudia Kasaw, MD, Paulo Chaves, MD, PhD, Sevil Yasar, MD, PhD, Patricia Smith, Joyce Chabot, John Hopkins University; John Robbins, MD, MHS, Katherine Gundling, MD, Sharene Theroux, CCRP, Lisa Pastore, CCRP, University of California-Davis; Lewis Kuller, MD, DrPH, Roberta Moyer, CMA, Cheryl Albig, CMA, University of Pittsburgh; Gregory Burke, MD, Steve Rapp, PhD, Dee Posey, Margie Lamb, RN, Wake Forest University School of Medicine. Schwabe Pharmaceuticals: Robert Hör, MD, Joachim Herrmann, PhD. Data Coordinating Center: Richard A. Kronmal, PhD, Annette L. Fitzpatrick, PhD, Fumei Lin, PhD, Cam Solomon, PhD, Alice Arnold, PhD, University of Washington, Cognitive Diagnostic Center: Steven DeKosky, MD, Judith Saxton, PhD, Oscar Lopez, MD, Beth Snitz PhD, M. Ilyas Kamboh PhD, Diane Ives, MPH, Leslie Dunn, MPH, University of Pittsburgh. Clinical Coordinating Center: Curt Furberg, MD, PhD, Jeff Williamson, MD, MHS; Nancy Woolard, Kathryn Bender, PharmD., Susan Margitic, MS, Wake Forest University School of Medicine, Central Laboratory: Russell Tracy, PhD, Elaine Cornell, UVM, University of Vermont. MRI Reading Center: William Rothfus MD, Charles Lee MD, Rose Jarosz, University of Pittsburgh. Data Safety Monitoring Board: 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, ND MHP, 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; Richard Shader, PhD, Tufts University.

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