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Diuretic Use is Associated with Better Learning and Memory in Older Adults in the GEM Study

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Abstract

Background—To investigate the association between diuretics, angiotensin-converting-enzyme inhibitors (ACE-I) and angiotensin 2 receptor blockers (AT2RB) and cognitive function.

Methods—This post-hoc analysis of the randomized controlled Ginkgo Evaluation of Memory Study trial focuses on 3069 non-demented community dwelling participants over the age of 75. At basline visit detailed information about medication use was collected and five cognitive domains were assessed. Multivariable linear regression analyses were used to assess cross-sectional associations between medication use and cognitive function.

Results—36% reported history of hypertension and 51% 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 (CVLT), compared to no antihypertensive medication users (β=.068, P=.01; β =.094, P<.001) and other antihypertensive medication users (β=.080, P=.03; β=.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.

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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 via 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, on cognitive function in hypertensive patients, and results have been mixed [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 type of antihypertensive medications, and cognitive function was often a secondary end point, measured by instruments designed to screen for cognitive impairment. However, one small clinical trial found that use of blood-brain barrier crossing ACE-Is decreased rate of global cognitive decline in subjects with AD [12]. In our recent study, diuretic and ACE-I use for more than 3 years was associated with reduced incidence of impairments in memory and executive function [13].

Based on 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 here whether 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 non-demented community dwelling participants, aged 75 years and older.

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 non-demented individuals aged 75 years and older 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 (NCCAM) and registered at clinicaltrials.gov (Trial Registration Identifier: NCT00010803). Details and results of the study have been previously published [14–16]. Due to 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, Maryland; Pittsburgh, Pennsylvania; Winston-Salem/Greensboro, North Carolina; and Sacramento, California. 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 or more were allowed to progress to a more rigorous battery

of 14 neuropsychologic 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. Comorbidities, including depressive symptoms, were ascertained and measured by the Center for Epidemiologic Studies Depression Scale (CES-D) [18], and medical history was based on self-report of a history of 16 diseases, including myocardial infarction, angina, stroke, transient ischemic attack, heart failure, hypertension, diabetes mellitus, 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. Names, doses, frequencies prescribed, frequencies actually taken in the prior 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, chlorthalidone, 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 (amiloride, spironolactone, triamterene) and those that were not (bumetanide, chlorthalidone, chlorothiazide, ethacrynic acid, furosemide, hydrochlorothiazide, indapamide, metolazone, methylchlorothiazide, torsemide), based on previous findings that only potassium-sparing diuretics decreased the incidence of AD [19, 20]. In addition, diuretics were also divided into thiazide diuretics (amiloride, chlorthalidone, chlorothiazide, hydrochlorothiazide, metolazone, methylchlorothiazide, spironolactone, triamterene), which are effective anti-hypertensive 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 (captopril, fosinopril, lisinopril, perindopril, ramipril, trandolapril) and those that do not cross the blood-brain barrier (benazepril, enalapril, moexipril, quinapril). This classification was used to address previous findings that use of blood-brain barrier crossing 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 assessed included attention, 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 Cognition Study [24, 25]. Here we assessed the associations of medications and global cognitive status (3MSE), verbal learning and memory (California Verbal Learning Test short [CVLT-FRS] and long delayed free recall [CVLT-FRL] [26]), and sum of trials 1 to 5 of List A [CVLT-Sum]), visuospatial construction (Modified Rey-Osterrieth Complex Figure Test copy [RO-Copy] [27]), visual learning and memory (Modified Rey-Osterrieth Complex Figure Test immediate [RO-IR] and delayed recall [RO-DR] [27]), attention and

psychomotor speed (Trail Making Test Part A [TMT, Part A] [28]), executive function (Trail Making Test, Part B [TMT, Part 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 non-demented participants at baseline, 362 (11%) were excluded because they reported concurrent use of ACE-I and diuretics (N=179) or ACE-Is and AT2RBs (N=1) or diuretics and AT2RBs (N=53) or beta blockers and diuretics (N=101) or vasodilators and diuretics (N=28), leading to a final sample of 2707 for comparative analyses. Of the 2707 subjects in the sample, 1318 reported no use of antihypertensive medications, 560 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 to non-drug (N) and other types of antihypertensive drug (O) treated participants using comparisons between groups for outcomes by ANOVA or Chi-square.

Multivariable 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, North Carolina), and unstandardized regression coefficients were reported. The results were considered significant if $P < .05$ in two-tailed comparisons.

In order 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 hypertension and its treatment we used non-drug 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 compared to 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 potassium-sparing (Ksparing) and non-potassium-sparing (KNsparing) diuretics. Similar analyses were carried out to evaluate the associations between ACE-I and AT2RB use on cognitive functions compared to the two different control groups. Analyses were then stratified according to use of blood-brain barrier crossing (BBBC) and blood-brain barrier non-crossing (BBBNC) ACE-I.

Analyses were adjusted for the potential confounding effects of age, gender, race (categorized as white vs. non-white), education (categorized as <12, =12, > 12 years of education), income (categorized as <$36,000/yr, $36,000–52,500/yr, >$52,500/yr) and of health related behaviors including smoking status (never, former, current) and alcohol consumption (per week (never, former, <1 drink/week, ≥1 drink/week, ≥1 drink/day and ≥2 drink/day). Analyses were also individually adjusted for comorbidities such as history of hypertension (HTN), history of stroke (CVA) or transient ischemic attack (TIA), history of diabetes mellitus (DM), history of congestive heart failure (CHF), history of coronary artery diseas(CAD), history of renal disease (measured by serum creatinine, mg/dL), depression (measured by using CES-D), Body Mass Index (BMI, Body Mass Index (kg/m^2), and mean systolic (SBP, mmHg) and diastolic blood pressure (DBP, mmHg).

3. Results

3.1. Participants

The mean age of the 2707 participants was 78.6 years, 55% were male, 96% were white and 64% had college education. 36% reported hypertension, and mean systolic (SD) and diastolic blood pressures were 135.32 (3.89) and 69.09 (0.9) mmHg, respectively. The prevalence of diabetes mellitus (DM), coronary artery disease (CAD), congestive heart failure (CHF) and cerebrovascular accident (CVA) was 8%, 18%, 1% and 3%, respectively (Table 1). The baseline means (SD) 3MS, CVLT-FRS and FRL scores, and TMT Part A and Part B times (sec) 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, while 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, while 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 to the non-drug group. All antihypertensive medication users, including other antihypertensive drug, diuretic, ACE-I and AT2RB users, had higher SBP compared to the non-drug group (Table 1). There were no significant differences in baseline characteristics between BBBC (N=207) and BBBNC ACE-I users (N=102) or between potassium-sparing (N=192) and non potassium-sparing diuretics users (N=267) (data not shown).

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 non-drug group did not differ in cognitive functions assessed, 3MS, TMT-A, TMT-B, CVLT-FSR, CVLT-FLR, CVLT-Sum, RO-IR, RO-DR, RO-Copy (3MSE: β=−.007, SE=.25, P=0.76; TMT-A: β=−.007, SE=.87, P=0.77; TMT-B: β=−.035, SE=2.3, P=0.13; CVLT-FSR: β=−.005, SE=.17, P=0.82; CVLT-FLR: β=−.019, SE=.17, P=0.43; CVLT-Sum: β=−.020, SE=.54, P=0.40; RO-IR: β=−.033, SE=.23, P=0.18; RO-DR: β=−.014, SE=.23, P=0.57; RO-COPY: β=−.017, SE=.15, P=0.48).

Diuretic use was associated with better verbal learning and memory (CVLT-FRS, CVLT-FRL and CVLT-Sum) when compared to non-drug group (β=.048, SE=.18, P=0.05; β=.048, SE=.18, P =0.05; β=.057, SE=.57, P =0.02, respectively) and other antihypertensive drug group (β=.053, SE=.21, P=0.1; β=.076, SE=.21P =0.02; β=.104, SE=.64, P<0.001, respectively) (Table 3). We then classified diuretic use according to the use of loop or thiazide diuretics and we found no association between loop or thiazide diuretics and cognitive functions. However, when diuretics were stratified according to the use of potassium-sparing (Ksparing) and non-potassium-sparing (KNsparing), we found that potassium sparing diuretics were responsible for the better performance on verbal learning and memory (CVLT-FRS, CVLT-FRL and CVLT-Sum) when compared to the non-drug group (β=.068, SE=.25, P =0.01; β=.094, SE=.25, P<0.001; β=.067, SE=.81, P =0.01, respectively) and other antihypertensive drug group (β=.080, SE=.28, P=0.03; β=.153, SE=.28, P<0.001; β=.126, SE=.85, P <0.001, respectively) (Table 3).

In contrast, we found no differences in any of the six cognitive outcomes between those receiving either ACE-Is and AT2RBs and those not receiving either ACE-Is and AT2RBs when compared to 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 non-demented, 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 potassium-sparing diuretic use was selectively associated with better performance on verbal learning and memory, compared to other and no antihypertensive medication users. Although observed associations were modest, they were highly significant and selectively.

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], while others showed no effect of ACE-Is [2, 4, 10, 30], thiazide diuretics [4, 31, 32], or AT2RBs [7, 10, 11]. These studies had weaknesses two key ways. First, they were unable to specify type of antihypertensive medications. Second, cognitive function was often a secondary end point, measured using blunt instruments designed to screen for cognitive impairment. Here, we extended our prior work in community elders 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 potassium-sparing diuretics on the development of AD [20] and on global cognitive decline in subjects with AD [19].

In this study, use of potassium-sparing diuretics was associated with better verbal learning and memory, when compared to no antihypertensive medication users, but also when compared to other antihypertensive medication users. The two control groups had either similar (other antihypertensive medication group) or lower (no antihypertensive medication group) systolic blood pressure than the diuretic users, which suggests 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 potassium-sparing 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 ours in non-demented older adults suggest involvement of low serum potassium levels in the neurodegenerative process of AD. One weakness of our study is that serum potassium level was unavailable, in order to evaluate its possible association with cognitive functions. Our findings could also be due to the fact that more women were using diuretics. However since 60% of potassium-sparing and also 60% of non-potassium-sparing diuretic users were women, gender cannot explain the positive associations on learning and memory of potassium-sparing diuretics.

Reported use of ACE-Is and AT2RBs was not associated with better cognitive functions confirming 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 more than 3 years was associated with a reduced incidence of cognitive impairment

[13] and another study where 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 a number of 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 employing 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 prior blood pressure levels, such as severity and length, and for medication use since we do not know what the participants were taking prior this study. The strength of exclusion of multiple antihypertensive medication users from our analysis may at the same time be a weakness, since 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, independently from history of hypertension or current blood pressure control.

This study also had some limitations, including its cross-sectional design which precludes assessment of protective 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 prior use of these medications. As in all observational studies, our results may also be vulnerable to confounding. We sought to address confounding by adjusting for history of HTN, CHF, DM and CAD, all of which are implicated in cognitive impairment and are main indications for use of diuretics, ACE-Is and AT2RBs. Additionally, in a separate analysis, we only included participants with a history of hypertension (N=1098) and were able to replicate our findings in the potassium-sparing diuretic user group when compared to non-drug (CVLT-FRS, β=.21, P =0.09; CVLT-FRL, β=.159, P=0.025; CVLT-Sum, β=.160, P=0.02) and other antihypertensive drug group (CVLT-FRS, β=.071, P=0.09; CVLT-FRL, β=.155, P<0.001; CVLT-Sum, β=.102, P=0.01). Another potential limitation is survival bias, since users of antihypertensive medications might be more likely to die due to increased mortality risk associated with hypertension; however, this was addressed by using a control group of non-drug users which had significantly lower blood pressures compared to all other groups. Additionally, since there is a large cost difference between potassium-sparing diuretics and AT2RBs compared to non-potassium sparing diuretics and ACE-Is, we can not rule out substantial residual confounding by socioeconomic status since our categories were based on income only.

In summary, this cross-sectional study found that use of potassium-sparing diuretic was associated with better verbal learning and memory in non-demented older individuals, suggesting a neuroprotective effect. The consistent and selective pattern of association between potassium sparring diuretic use and memory warrants further longitudinal investigations to evaluate possible protective effects of potassium-sparing 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 potassium-sparing diuretics, in order to determine clinical relevance. Longitudinal studies are also needed to determine if potassium sparing 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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Appendix

GEM Study Personnel

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Table 1

Demographics and Baseline Characteristics of Study Participants

	Overall	Non-drug group (C)	Other antihypertensive drug group (O)	ACE-I Users	Diuretic Users	AT2RB Users	*P*
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
N	2707	1318 (48)	560 (21)	309 (11)	459 (17)	61 (2)	
Age, mean (SD)		78.5 ± 3.3	78.7 ± 3.3	78.6 ± 3.1	78.8 ± 3.4	78.6 ± 3.5	.494
Gender							.000
Male	1476 (55)	688 (52)	380 (68)	196 (63)	182 (40)	30 (49)	
Race							.027
White	2593 (96)	1278 (97)	531 (95)	296 (96)	430 (94)	58 (95)	
Education							.063
<12 yr	293 (11)	135 (10)	53 (9)	34 (11)	61 (13)	10 (16)	
=12 yr	671 (25)	309 (23)	141 (25)	83 (27)	115 (25)	23 (38)	
>12 yr	1743 (64)	874 (66)	366 (65)	192 (62)	283 (62)	28 (46)	
Income							.133
<36000	706 (26)	329 (25)	148 (26)	89 (29)	125 (27)	15 (25)	
36000–52000	1332 (49)	648 (49)	269 (48)	135 (44)	245 (53)	35 (57)	
>52500	658 (25)	339 (26)	141 (25)	82 (27)	86 (19)	10 (16)	
Smoking							.043
Never	1080 (41)	538 (41)	208 (37)	109 (35)	204 (44)	21 (34)	
Former	1456 (54)	697 (53)	320 (57)	174 (56)	227 (49)	38 (62)	
Current	121 (5)	63 (5)	22 (4)	19 (6)	17 (4)	0 (0)	
Hx HTN	984 (36)	57 (4)	307 (55)	238 (77)	329 (72)	53 (87)	.000
Hx. DM	216 (8)	57 (4)	40 (7)	76 (25)	33 (7)	10 (16)	.000
Hx. CAD	481 (18)	116 (9)	180 (32)	76 (25)	92 (20)	17 (28)	.000
Hx. CVA	77 (3)	24 (2)	15 (2)	17 (6)	19 (4)	2 (3)	.003
Hx. TIA	189 (7)	50 (4)	55 (10)	32 (10)	43 (9)	9 (15)	.000
Hx. CHF	37 (1)	7 (1)	9 (2)	12 (4)	9 (2)	0 (0)	.000
Hx. AF	207 (8)	65 (5)	72 (13)	34 (11)	30 (7)	6 (10)	.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

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	Overall	Non-drug group (C)	Other antihypertensive drug group (O)	ACE-I Users	Diuretic Users	AT2RB Users	*P*
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
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 ± 9.4	69.2 ± 10.1	67.8 ± 10.9	68.8 ± 9.9	70.3 ± 10.5	.195
Se 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

Values listed are N (percentage) or mean ± s.d.

P values are comparisons across 5 groups by ANOVA or Chi-square.

ACE-I = Angiotensin Converting Enzyme Inhibitor, AT2RB = Angiotensin II Receptor Blocker.

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.

Table 2

Baseline Cognitive Characteristics of Study Participants

	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	93.1 ± 4.4	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

Values listed are mean ± s.d.

ACE-I = Angiotensin Converting Enzyme Inhibitor, AT2RB = Angiotensin II Receptor Blocker.

3MS = Modified Mini Mental State Exam; TMT-A = Trail Making Test, Part A; TMT-B = Trail Making Test, Part B; CVLT = California Verbal Learning Test (CVLT-FRS = short delayed free recall; CVLT-FRL = long delayed free recall; CVLT-Sum = 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).

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Table 3

Cross-Sectional Multivariate Linear Regression Association of Cognitive Function between Diuretic Users compared to No Antihypertensive Medication and Other Antihypertensive Medication Users

	N	3MS		TMT-A		TMT-B		CVLT-FRS		CVLT-FRL		CVLT-Sum		RO-IR		RO-DR		RO_Copy	
		β	SE	β	SE	β	SE	β	SE	β	SE	β	SE	β	SE	β	SE	β	SE
Diuretic vs. C	459	.028	.26	.017	.98	.043	2.51	.048*	.18	.048*	.18	.057**	.57	−.002	.25	−.019	.25	.033	.17
Diuretic vs. O		.026	.30	.021	1.17	.036	3.09	.053	.21	.076*	.21	.104***	.64	.021	.28	−.013	.28	.025	.19
Loop vs. C	111	−.052	.50	.007	1.81	.046	4.62	−.002	.34	.030	.34	.002	1.10	−.028	.47	−.051	.47	.016	.31
Loop vs. O		−.076	.53	.021	1.94	.047	5.17	−.012	.36	−.026	.36	.026	1.11	−.036	.47	−.087*	.47	.014	.31
Thiazide vs C	165	.023	.38	.018	1.40	.046	3.59	.017	.26	−.004	.26	.028	.84	−.002	.36	−.015	.36	.011	.24
Thiazide vs. O		.019	.42	.032	1.59	.051	4.24	.021	.28	.011	.29	.065	.89	.019	.39	−.019	.38	−.004	.26
Ksparing vs. C	192	.041	.36	.015	1.30	.014	3.43	.068**	.25	.094***	.25	.067**	.81	.006	.35	.004	.35	.026	.23
Ksparing vs. O		.049	.40	.007	1.44	−.004	4.05	.080**	.28	.153***	.28	.126***	.85	.024	.36	.015	.36	.018	.25
KNsparing vs. C	267	−.001	.32	.013	1.21	.054*	3.01	.010	.22	−.017	.22	.023	.71	−.010	.31	−.034	.31	.025	.20
KNsparing vs. O		−.011	.36	.032	1.41	.057	3.62	.011	.24	−.006	.24	.059	.76	−.008	.34	−.046	.33	.017	.22

β=beta coefficient, SE=standard error

3MS = Modified Mini Mental State Exam; TMT-A = Trail Making Test, Part A; TMT-B = Trail Making Test, Part B; CVLT = California Verbal Learning Test (CVLT-FRS = short delayed free recall; CVLT-FRL = long delayed free recall; CVLT-Sum = Sum of trials 1 to 5 of List A); RO = Modified Rey-Osterrieth Complex Figure Test (RO-IR = immediate recall; RO-DR = delayed recall; RO-Copy = Copy). C = No antihypertensive medication use; O = Other antihypertensive medication use (calcium channel blockers, beta blockers, others).

*$P < 0.05$,

**$P<0.01$,

***$P<0.001$.

Table 4

Cross-Sectional Multivariate Linear Regression Association of Cognitive Function between ACE-I and AT2RB Users Compared to No Antihypertensive Medication or Other Antihypertensive Medication Users

	N	3MS		TMT-A		TMT-B		CVLT-FRS		CVLT-FRL		CVLT-Sum		RO-IR		RO-DR		RO_Copy	
		β	SE	β	SE	β	SE	β	SE	β	SE	β	SE	β	SE	β	SE	β	SE
ACE-I vs. C	309	−.014	.31	.001	1.1	−.007	2.9	.018	.21	.011	.21	.001	.69	−.020	.30	−.012	.30	−.040	.20
ACE-I vs. O		−.020	.33	−.009	1.2	−.025	3.2	.029	.23	.034	.23	.009	.72	.009	.31	.004	.31	−.013	.21
ACE-I BBBC vs. C	207	−.007	.36	.005	1.3	−.011	3.3	.004	.25	.002	.25	−.011	.81	−.028	.35	−.023	.35	−.015	.23
ACE-I BBBC vs. O		.011	.38	−.002	1.3	−.023	3.7	.009	.26	.021	.27	−.010	.82	−.002	.35	−.009	.36	−.021	.23
ACE-I BBBNC vs C	102	−.015	.49	−.008	1.7	−.004	4.5	.031	.33	.016	.33	.022	1.1	−.001	.47	.008	.46	.012	.30
ACE-I BBBNC vs. O		−.026	.51	−.016	1.8	−.019	5.0	.039	.35	.038	.35	.034	1.1	.017	.46	.021	.45	.009	.30
AT2RB vs. C	61	−.027	.62	−.009	2.2	−.001	5.7	.026	.42	.028	.42	.016	1.4	−.011	.59	.008	.59	.004	.38
AT2RB vs. O		−.063	.64	−.020	2.3	−.014	6.3	.024	.43	.036	.44	.016	1.4	−.019	.58	−.006	.57	−.029	.38

β =beta coefficient, SE=standard error

3MS = Modified Mini Mental State Exam; TMT-A = Trail Making Test, Part A; TMT-B = Trail Making Test, Part B; CVLT = California Verbal Learning Test (CVLT-FRS = short delayed free recall; CVLT-FRL = long delayed free recall; CVLT-Sum = Sum of trials 1 to 5 of List A); RO = Modified Rey-Osterrieth Complex Figure Test (RO-IR = immediate recall; RO-DR = delayed recall; RO-Copy = Copy).

C = No antihypertensive medication use; O = Other antihypertensive medication use (calcium channel blockers, beta blockers, others).

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