Antihypertensive Therapy and Cerebral Hemodynamics in Executive Mild Cognitive Impairment: Results of a Pilot Randomized Clinical Trial

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OBJECTIVES: To compare the effects of three antihypertensive medications on cerebral hemodynamic and cognitive function in hypertensive individuals with executive dysfunction.

DESIGN: Double-blind randomized clinical trial.

SETTING: Community.

PARTICIPANTS: Fifty-three individuals aged 60 and older with hypertension and executive dysfunction.

INTERVENTION: Lisinopril, candesartan, or hydrochlorothiazide for 1 year.

MEASUREMENTS: Cerebral blood flow velocity (BFV; transcranial Doppler ultrasonography during rest, sitting, standing, hypercapnia, and hypocapnia), cognition, and blood pressure were measured at baseline and after 6 and 12 months. Linear mixed models were used to compare the three groups.

RESULTS: Of the 53 participants, 47 had successful insonation (mean age 72; 70% white; 57% women). There was a tendency toward an increase in BFV in the candesartan group and a decrease in the lisinopril and hydrochlorothiazide groups (between-group $P = .57$) that was significant in those with low BFV at baseline (<median 27.6 cm/s, between-group $P = .03$). The candesartan group also had the greatest improvement in executive function (Trail Making Test Part B improved by 17.1 seconds, vs hydrochlorothiazide improved by 4.2 seconds and lisinopril worsened by 14.4 seconds, $P = .008$). Carbon dioxide vasoreactivity and vasomotor range declined significantly in the lisinopril (within-group $P = .001$ for vasoreactivity and .02 for vasomotor range) and hydrochlorothiazide groups (within-group $P = .10$ and .009, respectively) but not in the candesartan group (within-group $P = .25$ and .38, respectively; between-group $P = .30$ and .46, respectively).

CONCLUSION: Angiotensin receptor blockers may preferentially preserve cerebral hemodynamics and executive function in individuals with executive dysfunction. These findings warrant further investigation in a larger trial. **J Am Geriatr Soc 2013.**

Key words: angiotensin receptor blocker; cerebrovascular circulation; executive function hemodynamics; hypertension

Hypertension is associated with cognitive impairment, especially in the executive domain.[1–3] Individuals with hypertension who develop executive dysfunction have similar mortality and institutionalization rates as those with dementia[4] and greater mortality and disability than individuals with hypertension without executive dysfunction.[5] Hypertension is also associated with lower cerebral blood flow velocity (BFV) and cerebrovascular reserve as assessed by vasoreactivity to carbon dioxide (CO_2).[6,7] Impaired cerebral blood flow may further contribute to cognitive decline.[8] The differential effect of antihypertensive medications on cerebral hemodynamics especially in the context of executive dysfunction is not well investigated.

Recent evidence suggests that the renin angiotensin system (RAS) is involved in the regulation and maintenance of cerebral blood flow.[9] In hypertension, angiotensin II decreases cerebral blood flow[10] and impairs neurovascular coupling.[9] Previous work suggests that polymorphisms in RAS genes are associated with cerebral vasoreactivity to CO_2.[11] In the brain, angiotensin II

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exerts its main effects by activating two receptors: type 1, which leads to vasoconstriction, endothelial dysfunction, and vascular remodeling, and type 2, which leads to vasodilatation, neuronal differentiation, lower inflammation, and axonal regeneration.[12] Angiotensin receptor blockers (ARBs) block the type 1 but not type 2 receptors, whereas angiotensin-converting enzyme inhibitors (ACEIs) decrease angiotensin II production and hence decrease activation of both receptors. It was therefore hypothesized that an ARB-based regimen would have greater positive effects on cerebral hemodynamics and executive function than other antihypertensive treatments, including ACEIs.

The objective was to conduct a double-blind randomized clinical trial comparing the effects of an ARB (candesartan), an ACEI (lisinopril), and an active control (hydrochlorothiazide) on cerebral blood flow, cerebrovascular reserve and hemodynamics, and executive function in individuals with hypertension with executive cognitive impairment without dementia.

METHODS

The study design is fully described elsewhere.[13] Briefly, this was a 12-month double-blind randomized controlled clinical trial of candesartan, lisinopril, or hydrochlorothiazide. Inclusion criteria were aged 60 and older, hypertension (systolic blood pressure (SBP) $\geq$140 mmHg or diastolic blood pressure (DBP) $\geq$90 mmHg or receiving antihypertensive medications), and executive dysfunction based on a score less than 10 on the executive clock draw test (CLOX1).[14] To exclude individuals with possible dementia, those with a Mini-Mental State Examination (MMSE) score less than 20[15] or with a clinical diagnosis of Alzheimer's disease or other dementia were not enrolled. Exclusion criteria were intolerance to the study medications; SBP greater than 200 mmHg, DBP greater than 110 mmHg; serum creatinine greater than 2.0 mg/dL or serum potassium greater than 5.3 mEq/dL at baseline; receiving more than two antihypertensive medications; presence of congestive heart failure, diabetes mellitus, or stroke; and inability to perform the study procedures or unwilling to stop currently used antihypertensive medications. Antihypertensive medications were tapered using a standard protocol described elsewhere.[13]

Participants were recruited from the greater Boston area using newspaper announcements, mailed fliers, and blood pressure screening activities in the general community. After approval of their primary care providers, participants receiving antihypertensive medications were tapered and stopped over 3 weeks. Baseline measurements (off antihypertensive medications) of blood pressure, cognitive function, physical performance, and cerebral blood flow hemodynamics using transcranial Doppler (TCD) procedures were then completed. Randomization using a computer-generated random allocation sequence occurred after baseline data collection. Participants were seen every 2 weeks until blood pressure control (<140/90 mmHg) was achieved. The institutional review board of Hebrew SeniorLife approved the study, and all participants provided written informed consent. The study was registered in ClinicalTrials.gov (NCT00605072).

The Intervention

Participants were treated with lisinopril (10 mg increased to 20 mg then 40 mg if needed), candesartan (8 mg increased to 16 mg then 32 mg if needed), or hydrochlorothiazide (12.5 mg increased to 25 mg if needed). The goal of the intervention was to achieve SBP less than 140 mmHg and DBP less than 90 mmHg. If this goal was not achieved after maximum doses of the study drugs, long-acting nifedipine (30 mg increased to 60 and 90 mg) was added, followed by long-acting metoprolol (12.5 mg increased to 25 and 50 mg).

Study Procedures

Baseline and 6- and 12-month assessments included questionnaires asking about social habits, family history, and self-reported medical history; a medication inventory; height; weight; amount of physical activity according to the Physical Activity Scale for the Elderly,[16] and functional status according to instrumental activities of daily living (IADLs).[17] Blood pressure was measured according to the American Heart Association guidelines.[18] Two seated blood pressure readings were performed and averaged at each visit. The cognitive battery was described previously and included the Trail Making Test (TMT), the Hopkins Verbal Learning Test—Revised (HVLT), and the Digit Span Test.[13]

Cerebral Blood Flow Hemodynamics

Cerebral BFV was measured at the middle cerebral artery using TCD ultrasonography (2-MHz probe placed over the temporal bone, MultiDop X4; DWL-Transcranial Doppler Systems, Inc., Sterling, VA). End-tidal CO_2 was measured using a CO_2 analyzer (Vacumed, Ventura, CA) attached to a nasal cannula. Mean BFV was measured at rest, during changes in end-tidal CO_2 (breathing a gas with 8% CO_2 for 2 minutes and then mildly hyperventilated to an end-tidal CO_2 of approximately 25 mmHg for 2 minutes); and blood pressure changes during a sit-to-stand protocol.[19] Beat-to-beat heart rate and blood pressure were simultaneously measured using continuous ECG recording and a noninvasive continuous blood pressure measuring instrument (Finometer; Finapres Measurement Systems, Arnhem, the Netherlands). Data were analyzed offline using Matlab (Mathworks, Natick, MA). Cerebrovascular resistance (CVR) was calculated as mean arterial pressure divided by BFV. The difference between sitting and standing CVR ($\Delta CVR = CVR_{stand} - CVR_{sit}$) was used as an indicator of autoregulation. Vasoreactivity was calculated as the slope of the regression between mean BFV and end-tidal CO_2 at the time elapsing between two consecutive R waves in the electrocardiogram. Vasomotor range (VMR) was computed as the increment between minimum mean BFV during hyperventilation and maximum BFV during CO_2 breathing. Both measures were used as indicators of cerebrovascular reserve.

Statistical Analysis

Baseline comparisons between the three randomized groups were performed to evaluate randomization effectiveness

using analyses of variance (ANOVAs) or chi-square tests. An intention-to-treat analysis was used. Linear mixed models for repeated measures were used to compare the progression of outcomes in the three groups. Age-adjusted least square means were computed for each visit according to treatment group; differences between least square means provided tests of mean differences within (change over visits) and between groups. A predefined subgroup analysis was performed for those with low baseline BFV to test the hypothesis that ARBs would improve perfusion in those with significant baseline hypoperfusion (defined below as the median of the enrolled sample). To explore whether the change in executive function was related to changes in cerebral hemodynamics, those with stable executive function over the study period (defined as no change or improved scores on the TMT Part B) and those with stable cerebral hemodynamics (defined as no change or improved BFV, CO_2-vasoreactivity, and VMR during the study period) were first characterized. For those who did not have TCD data at 12 months, the measure at 6 months was used to characterize their change. A concordance rate was calculated within each treatment group as the proportion of participants with stable cognitive function and stable hemodynamics divided by the number of individuals treated within that group. A higher concordance rate may suggest a greater contribution of hemodynamics to the executive cognitive change. The Cochran–Mantel–Haenszel statistic was used to test the hypotheses that the concordance rates between the three groups differed.[20]

RESULTS

Fifty-three of the 63 eligible participants were successful in tapering their antihypertensive medications and were randomized; 47 of those (89%) had successful insonation of the middle cerebral artery. Forty-seven of the 53 randomized completed 6-month (40 had successful TCD insonation), and 31 completed 12-month evaluations (29 had successful TCD insonation). This analysis was restricted to those with successful insonation at baseline (n = 47). A participant flowchart is provided in an online figure (Figure S1). As shown in Table 1, the three groups were similar in all baseline clinical characteristics, blood pressure, and cerebral hemodynamics. They also had similar reported adverse events, as shown in Table 2.

Blood Pressure Control

Systolic blood pressure reductions were equivalent in all three groups (mean reduction (standard error): lisinopril group, 27 ± 5 mmHg; candesartan, 26 ± 5 mmHg; hydrochlorothiazide, 25 ± 6 mmHg; $P = .93$). Blood pressure control levels were also equivalent (lisinopril, 91%; candesartan, 100%; hydrochlorothiazide, 100%; $P = .40$). The average number of visits to achieve control was lowest for candesartan (1.3 vs 2.5 for lisinopril and 2.0 for hydrochlorothiazide; $P < .001$).

Resting Cerebral BFV

The three groups did not differ in baseline cerebral hemodynamic measures. There was a trend toward an increase in BFV (increase of 1.03 cm/s over 12 months) in the candesartan group, whereas there was a decline in the lisinopril group of 2.12 cm/s and in the hydrochlorothiazide group of 2.40 cm/s. The between-group *P*-value was .57, although in those with low BFV (<the median of 27.6 cm/s) at baseline (n = 23), the candesartan effect was more pronounced (BFV increased by 2.79 cm/s in the candesartan group vs decline in the lisinopril and hydrochlorothiazide groups) (between-group $P = .03$) (Figure 1).

Orthostatic Hemodynamics and Autoregulation

Despite the significant decreases in sitting blood pressure after treatment, there were no increases in the 1- and 3-minute orthostatic blood pressure declines in the three groups (Table 3). Furthermore, the BFV declines during active standing did not worsen in all three groups, although there was a group difference in orthostatic changes in CVR; those treated with candesartan or lisinopril showed less change in CVR upon standing, whereas those treated with hydrochlorothiazide showed greater change in CVR upon standing (between-groups $P = .05$) (Table 4).

Cerebrovascular Reserve

As shown in Table 4, participants treated with candesartan had no significant decline in vasoreactivity (within-group *P* for trend = .25) or vasomotor range ($P = .38$) over the 12-month period; in contrast, subjects randomized to lisinopril and hydrochlorothiazide had declines in both measures over the study period (vasoreactivity: $P = .001$ for lisinopril and .1 for hydrochlorothiazide; VMR: $P = .02$ for lisinopril and .009 for hydrochlorothiazide). The between-group comparisons did not reach statistical significance ($P = .30$ for vasoreactivity and .46 for VMR).

Executive Function and Cerebral Hemodynamics

After adjusting for age and baseline MMSE, those randomized to candesartan demonstrated the greatest improvement in TMT Part B (12-month least square mean decrease of 17.1 seconds vs a decrease of 4.2 seconds in the hydrochlorothiazide group and an increase of 14.4 seconds in the lisinopril group, between-group $P = .008$). Those in the candesartan group also showed improved performance on the recognition portion of the HVLT, which assesses in part aspects of executive function (between-group $P = .03$). There were no group differences in change in HVLT immediate and delayed recall or in the Digit Span Test. In the candesartan group, 8 (47%) had stable or improved executive function and BFV, versus 3 (18%) in the lisinopril group and 1 (13%) in the hydrochlorothiazide group. These group differences did not reach statistical significance ($P = .71$). The concordance rate tended to be highest in the candesartan group for VMR (candesartan, 3 (18%); lisinopril, 1 (6%), hydrochlorothiazide, 2 (15%); $P = .39$) but not CO_2 vasoreactivity (hydrochlorothiazide, 4 (31%); candesartan, 3 (18%); lisinopril, 1 (6%); $P = .78$). Because of the small number of individuals in each group, these results should be interpreted with great caution.

Table 1. Baseline Characteristics, Sitting and Orthostatic Blood Pressure, and Cerebral Hemodynamics of Those Randomized and with Successful Transcranial Doppler Insonation According to Study Group

Measure	Lisinopril, n = 17	Candesartan, n = 17	Hydrochlorothiazide, n = 13	*P*-Value[a]
Age, mean ± SD	72 ± 6	72 ± 9	71 ± 7	.91
Female, %	59	47	69	.47
African American, %	29	12	31	.71
White, %	65	82	62	
Education, %				
≤ High school	18	24	15	.84
≥ College education	82	76	84	
Body mass index, kg/m^2, mean ± SD	29.1 ± 5.9	28.1 ± 4.1	29.0 ± 7.9	.87
Baseline cognitive function, mean ± SD				
Mini-Mental State Examination	26 ± 2	26 ± 2	25 ± 2	.15
Executive Clock Drawing test	9 ± 2	9 ± 2	9 ± 2	.80
Baseline functional and mood measures, mean ± SD				
Gait speed, m/s	1.17 ± 0.21	1.12 ± 0.38	1.03 ± 0.21	.44
Instrumental activities of daily living	8 ± 0	8 ± 0	8 ± 0	.60
Physical Activity Scale in the Elderly	179 ± 59	150 ± 61	175 ± 52	.33
Center for Epidemiologic Studies Depression Scale	8 ± 7	8 ± 7	6 ± 6	.81
Baseline biochemical profile, mean ± SD				
Serum creatinine, mg/dL	0.90 ± 0.25	1.00 ± 0.24	0.88 ± 0.30	.37
Serum Potassium, mEq/dL	4.46 ± 0.37	4.47 ± 0.32	4.41 ± 0.45	.89
Medications, %				
Aspirin	35	29	30	.93
Statin	24	41	31	.54
Prestudy antihypertensive medication, %				
Diuretic	41	24	31	.54
Angiotensin-converting enzyme inhibitor, %	29	29	31	.99
Angiotensin receptor blocker	29	0	23	.06
Calcium channel blocker	0	18	8	.18
Beta-blockers	24	12	38	.23
Relevant medical history, %				
Coronary artery disease	35	56	46	.48
Hyperlipidemia	35	56	38	.44
Blood pressure and heart rate				
Sitting				
SBP, mmHg	153 ± 18	149 ± 13	155 ± 15	.60
DBP, mmHg	85 ± 10	81 ± 8	83 ± 8	.41
Heart rate, beats per minute	64 ± 11	65 ± 8	66 ± 9	.82
Sit-to-stand after 1 minute[b]				
SBP, mmHg	−4 ± 7	−10 ± 10	−10 ± 6	.10
DBP, mmHg	1 ± 5	−2 ± 7	−3 ± 4	.19
Heart rate, beats per minute	2 ± 4	2 ± 6	1 ± 5	.91
Sit-to-stand after 3 minutes[b]				
SBP, mmHg	1 ± 6	−1 ± 10	−1 ± 5	.78
DBP, mmHg	3 ± 5	−2 ± 6	−0.1 ± 4	.02
Heart rate, beats per minute	2 ± 4	2 ± 5	2 ± 3	.96
Cerebral hemodynamics				
Sitting BFV, cm/s	28.1 ± 6.2	29.1 ± 5.7	29.8 ± 10.6	.81
Orthostatic change[b] in BFV, cm/s	−3.1 ± 2.5	−4.0 ± 3.5	−3.6 ± 2.6	.69
Sitting CVR, mmHg/cm per second	3.5 ± 0.8	3.4 ± 1.1	3.4 ± 1.2	.99
Orthostatic change[b] in CVR, mmHg/cm per second	−.50 ± 0.60	−0.26 ± 0.74	−0.35 ± 0.39	.54
CO_2 vasoreactivity, slope	0.56 ± 0.20	0.51 ± 0.16	0.59 ± 0.41	.71
CO_2 vasomotor range	0.61 ± 0.22	0.60 ± 0.22	0.72 ± 0.41	.50

[a] From analysis of variance for continuous variables and chi-square test for categorical variables.
[b] Standing measure–sitting measure.
SBP = systolic blood pressure; DBP = diastolic blood pressure; BFV = blood flow velocity; CVR = cerebrovascular resistance; CO_2 = carbon dioxide.

DISCUSSION

In this pilot study, it was found that an ARB-based regimen in older adults with hypertension and mild executive dysfunction may be associated with preserved executive function and BFV, especially in those with lower pretreatment BFV. These effects may contribute to the positive effects of candesartan on executive function. ARB treatment was also associated with preservation of cerebrovascular reserve, measured according to CO_2 vasoreactivity and VMR, whereas an ACEI- or diuretic-based regimens might not have provided this protection. Finally, better blood pressure control was not associated with greater orthostatic hypotension or orthostatic declines in BFV.

Table 2. Most Common Adverse and Serious Adverse Events Reported During the Study Period in All Participants (with and without Successful TCD Insonation)

Adverse Event	Lisinopril, n = 18	Candesartan, n = 20	Hydrochlorothiazide, n = 15	*P*-Value[a]
	%			
Dizziness	28	30	40	.73
Weakness or fatigue	17	5	7	.43
Fall, noninjurious	22	5	13	.29
Cough	28	20	20	.81
Hospitalization (nonelective) during study period[b]	22	15	20	.84

[a] From chi-square test.

[b] Reasons for hospitalization included pneumonia, chest pain, and leg pain from a traumatic muscle injury.

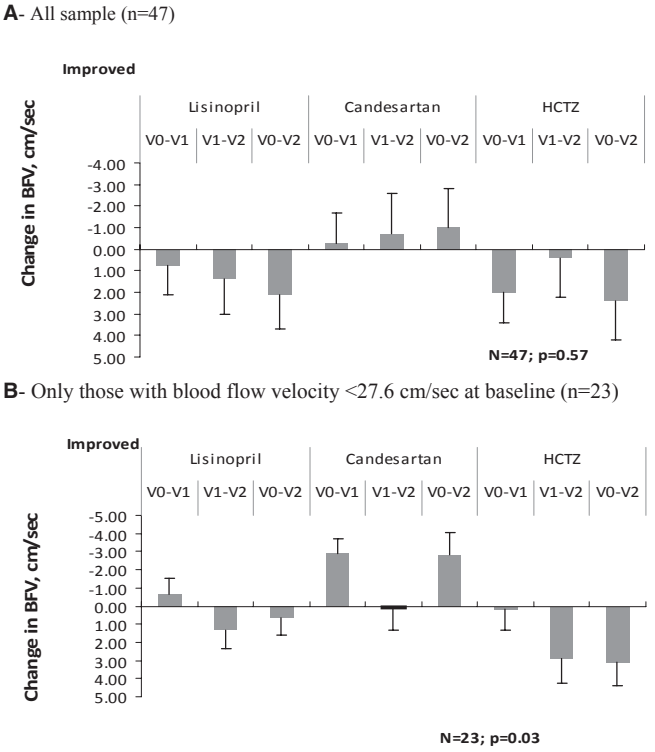

Figure 1. Changes over study period in the three groups in cerebral blood flow velocity (BFV) in the overall sample (A) and in those with baseline BFV below the median. Least square means were adjusted for age. *P*-values were obtained from the linear mixed model for the visit-by-group interaction parameter. V0–V1 = change from baseline to 6 months; V0–V2 = change from baseline to 12 months; V1–V2 = change from 6 months to 12 months. (A) Overall sample (n = 47), (B) only those with BFV <27.6 cm/s at baseline (n = 23).

To the knowledge of the authors, this is the first head-to-head comparison of the effects of three commonly used antihypertensive medications on cerebral hemodynamics in older adults with hypertension. Prior animal studies have suggested that ARBs improve cerebral blood flow, increase cerebrovascular reserve, and ameliorate ischemic changes from atherosclerosis and hypoperfusion.[21–25] In humans, two studies have shown that ARB treatment preserves or improves cerebral hemodynamics in individuals after stroke and in those with cerebral small-vessel disease.[26,27] The current study findings further extend these possible positive effects of ARBs to individuals who have not experienced a stroke.

Recent evidence suggests that there is an alternative pathway in the brain RAS that may counterbalance the negative effects of AT_1 through the activation of AT_2.[28–30] It was previously hypothesized that ARBs may have an effect superior to that of ACEIs because ARBs but not ACEIs are associated with AT_2 activation. The current study provides preliminary human support that AT_2 activation in the brain may be beneficial for executive function and cerebral hemodynamics.

This study suggests that candesartan may have a positive effect on executive function in those with existing limitations in this cognitive domain.[31] Decline in perfusion is associated with executive dysfunction,[32–34] and a decrease in CO_2 vasoreactivity has been observed in individuals with dementia.[35,36] There was a trend toward a higher degree of concordance between improved or unchanged scores on the TMT and BFV and VMR in participants treated with candesartan. Hence, the differential effect of ARBs on BFV and cerebrovascular reserve may have a role in the differential effects of ARBs relative to other antihypertensives on executive function, but these results need to be interpreted with caution because of the sample size within each group.

Antihypertensive therapy was not associated with greater orthostatic blood pressure or BFV reductions despite a decrease of 21–28 mmHg in sitting SBP after treatment. There was a trend toward less orthostatic decline in blood pressure and BFV. Clinically, this study suggests that achieving blood pressure control to less than 140/90 mmHg is unlikely to lead to a decline in cerebral blood flow or orthostatic hypotension, but because of the small sample size, these findings should be interpreted cautiously.

The mechanisms of these potential superior cerebrovascular effects of ARB may be related to restoring proper central endothelial function, decreasing inflammation, and preventing neuronal degeneration, partially through an activated AT_2-receptor pathway.[24,37–39] This unique effect of ARBs on AT_2 needs further investigation and may offer new therapeutic paradigm for vascular brain disease and cognitive dysfunction.

The main limitation of this study is the small sample size because this was a pilot study, and a larger clinical trial is needed to further confirm the findings. The validity of TCD measurements as an index of cerebral blood flow is based on the assumption that cerebral vessel diameters are constant.[40] Because brain imaging was not available, the ability to validate this assumption over the study period was limited.

Table 3. Sitting and Orthostatic Changes in Blood Pressure and Heart Rate in the Three Groups During the Study Period

	Lisinopril, n = 17	Candesartan, n = 17	Hydrochlorothiazide, n = 13	
Measure	**Age-Adjusted Least Square Mean (Standard Error)**			**Between-Group *P*-Value**
Sitting				
SBP, mmHg				
Baseline	153 (3)	150 (3)	156 (3)	.93
6 months	129 (4)	130 (4)	132 (4)	
12 months	126 (4)	124 (5)	131 (5)	
Within-group *P*-value	<.001	0.0001	<.001	
DBP, mmHg				
Baseline	85 (2)	81 (2)	83 (2)	.63
6 months	72 (2)	71 (2)	76 (2)	
12 months	70 (3)	69 (3)	74 (3)	
Within-group *P*-value	<.001	.001	.03	
Heart rate, bpm				
Baseline	64 (2)	65 (2)	66 (3)	.28
6 months	63 (3)	67 (3)	64 (3)	
12 months	65 (3)	63 (4)	73 (4)	
Within-group *P*-value	.74	.58	.09	
1-minute orthostatic change[a]				
SBP, mmHg				
Baseline	−5 (2)	−10 (2)	−10 (2)	.77
6 months	−3 (2)	−7 (3)	−4 (3)	
12 months	−3 (3)	−9 (3)	−4 (3)	
Within-group *P*-value	.71	.59	.08	
DBP, mmHg				
Baseline	1 (2)	−2 (2)	−3 (2)	.24
6 months	−2 (2)	−2 (2)	−1 (2)	
12 months	−1 (2)	−5 (3)	3 (3)	
Within-group *P*-value	.36	.73	.20	
Heart rate, bpm				
Baseline	2 (1)	2 (1)	1 (1)	.66
6 months	5 (1)	3 (1)	5 (1)	
12 months	5 (2)	4 (2)	6 (2)	
Within-group *P*-value	.06	.67	.04	
3-minute orthostatic change[a]				
SBP, mmHg				
Baseline	1 (2)	−1 (2)	−1 (2)	.78
6 months	4 (2)	−2 (3)	1 (2)	
12 months	2 (2)	−2 (4)	−2 (3)	
Within-group *P*-value	.43	.84	.65	
DBP, mmHg				
Baseline	3 (1)	−2 (1)	0 (1)	.16
6 months	1 (1)	1 (2)	2 (2)	
12 months	2 (2)	3 (2)	4 (2)	
Within-group *P*-value	.65	.04	.17	
Heart rate, bpm				
Baseline	2 (1)	2 (1)	2 (1)	.27
6 months	3 (1)	3 (1)	3 (1)	
12 months	3 (1)	2 (2)	8 (2)	
Within-group *P*-value	.48	.89	.03	

[a] Standing measure–sitting measure.

CONCLUSION

In this pilot study of older adults with hypertension and evidence of executive dysfunction, an ARB-based regimen may be associated with better cerebral blood flow and maintenance of cerebrovascular reserve than ACEI- or hydrochlorothiazide-based regimens. These positive effects on cerebral hemodynamics may partially contribute to the improved executive function observed with candesartan, but these findings should be considered cautiously because of the small sample size of this pilot study. Because no treatment is available for executive dysfunction, future studies exploring the effects of ARBs on executive cognitive impairment is a critical priority.

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Table 4. Age-Adjusted Least Square Mean of the Hemodynamic and Cerebrovascular Reactivity Measures in the Three Groups over the Study Period

	Lisinopril, n = 17	Candesartan, n = 17	Hydrochlorothiazide, n = 13	
Measure	**Age-Adjusted Least Square Mean (Standard Error)**			**Between-Group *P*-Value**
Sitting BFV, cm/s				
Baseline	28.00 (1.49)	29.12 (1.57)	29.52 (1.79)	.57
6 months	27.27 (1.58)	29.40 (1.68)	27.52 (1.78)	
12 month	25.89 (1.80)	30.13 (2.02)	27.12 (2.10)	
Within-group *P*-value	.43	.85	.27	
Standing change in BFV, cm/s				
Baseline	−3.10 (0.55)	−4.00 (0.74)	−3.46 (0.72)	.81
6 months	−3.26 (0.61)	−3.61 (0.80)	−2.92 (0.72)	
12 month	−2.84 (0.74)	−2.28 (0.99)	−2.38 (0.92)	
Within-group *P*-value	.88	.20	.51	
Sitting CVR, mmHg × s/cm				
Baseline	3.48 (0.20)	3.46 (0.22)	3.52 (0.24)	.70
6 months	2.97 (0.22)	2.81 (0.24)	3.26 (0.24)	
12 month	3.02 (0.26)	3.04 (0.30)	3.55 (0.31)	
Within-group *P*-value	.07	.03	.51	
Standing change in CVR, mmHg*s/cm				
Baseline	−0.50 (0.17)	−0.26 (0.17)	−0.35 (0.19)	.05
6 months	−0.85 (0.19)	−0.24 (0.19)	−0.44 (0.19)	
12 month	−0.14 (0.23)	−0.23 (0.25)	−0.89 (0.25)	
Within-group *P*-value	.03	.99	.17	
CO_2 vasoreactivity, slope				
Baseline	0.55 (0.05)	0.51 (0.06)	0.59 (0.06)	.30
6 months	0.42 (0.05)	0.48 (0.06)	0.47 (0.06)	
12 month	0.32 (0.06)	0.39 (0.08)	0.50 (0.07)	
Within-group *P*-value	.001	.25	.10	
CO_2 vasomotor range				
Baseline	0.61 (0.06)	0.61 (0.06)	0.72 (0.07)	.46
6 months	0.51 (0.06)	0.53 (0.07)	0.51 (0.07)	
12 month	0.39 (0.07)	0.50 (0.09)	0.56 (0.08)	
Within-group *P*-value	.02	.39	.009	

Values are obtained from the Mixed Model adjusted for age at baseline. Between group *P*-value is obtained from the Mixed Model output of the Group*-visit term, and within-group *P*-values is obtained from the Mixed Model.

BFV = blood flow velocity; CVR = cerebrovascular resistance; CO_2 = carbon dioxide.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Number of subjects enrolled and followed during the study period (number between brackets are those with successful insonation).

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