Denmark; Yafei Li, Third Military Medical University, Chongqing, China; Zhihong Cui, Third Military Medical University, Chongqing, China; Rosa Molina, Laboratorio de Andrologia y Reproduccion, Córdoba, Argentina; Ruben Daniel Ruiz, Facultad de Ciencias Medicas, Universidad Nacional de Córdoba, Córdoba, Argentina; Thomas L. Toth, Harvard Medical School, Boston, Massachusetts; Russ Hauser, Harvard School of Public Health, Boston; Janos Szollosi, University of Szeged, Szeged, Hungary; Ane Marie Thulstrup, Aarhus University Hospital, Aarhus, Denmark; Joop Laven, Marijana Vujkovic, and Fatima Hammiche, Erasmus University Medical Center, Rotterdam, the Netherlands; Gregor Majdic, Center for Animal Genomics, Veterinary Faculty, University of Ljubljana, Ljubljana, Slovenia; Rosana Hernandez Weldon, UC Berkeley School of Public Health, Berkeley, California; Andrew J. Wyrobek, Lawrence Berkeley National Laboratory, Berkeley; Department of Assisted Reproduction, Landspitali University Hospital, Landspitali, Iceland; and Zoltan Zavaczki, Landstinget Gavleborg, Hudiksvall, Sweden.

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Effect of Antihypertensive Therapy on Cognitive Function in Early Executive Cognitive Impairment: A Double-blind Randomized Clinical Trial

Approximately 50% of older hypertensive individuals have difficulties in executive function, the cognitive domain that controls complex tasks.[1] Hypertensive individuals with executive dysfunction have a high rate of conversion to dementia.[2] To our knowledge, to date, no study has investigated therapeutic options for executive dysfunction. Recent evidence suggests that the renin angiotensin system plays a central role in linking hypertension to cognitive function, offering new therapeutic options for cognitive protection.[3] In the brain, angiotensin receptor blockers (ARBs) block the type 1 but not the type 2 receptor, whereas angiotensin-converting enzyme inhibitors (ACEIs) decrease activation of both receptors. Activating the type 2 receptor may provide cognitive protection.[4] We therefore hypothesized that an ARB-based regimen would be superior to other antihypertensive regimens in cognitive protection, especially executive function, and conducted a 12-month double-blind randomized clinical trial comparing candesartan, lisinopril, and hydrochlorothiazide in hypertensive individuals with early executive dysfunction.

Methods. The study design is fully described elsewhere.[5] Subjects were recruited from the greater Boston area, Massachusetts, and were 60 years or older, had hypertension (systolic blood pressure >140 mm Hg and diastolic blood pressure >90 mm Hg), and demonstrated evidence of executive dysfunction based on the executive clock draw test (CLOX1 score <10). We excluded those with a Mini-Mental State Examination (MMSE) score lower than 20 or those with a clinical diagnosis of dementia, diabetes mellitus, stroke, or congestive heart failure. Antihypertensive medications were tapered using a standard protocol described elsewhere.[5] Randomization using a computer-generated random allocation sequence occurred after baseline data collection, and participants were seen every 2 weeks until their blood pressure was controlled (<140/90 mm Hg). Participants were treated with escalating doses of lisinopril, candesartan, or hydrochlorothiazide to achieve a blood pressure lower than 140/90 mm Hg. Long-acting nifedipine and long-acting metoprolol succinate were added if the goal blood pressure was not achieved. Cognitive assessments were repeated at 6 and 12 months and included Trail-Making Test (TMT) parts A and B, which assesses executive function; Hopkins Verbal Learning Test–Revised (HVLT), which assesses memory; and the Digit Span Test, which assesses attention. The Hebrew SeniorLife institutional review board approved the study, and written informed consent was obtained. An intention-to-treat analysis was performed, and linear mixed models for repeated measures were used to compare the progression of cognitive outcomes in the 3 groups. Least-square means adjusted for age and baseline MMSE score were computed for each visit by treatment group.

Results. Of the 63 eligible individuals screened, 53 stopped their antihypertensive medications and were randomized to lisinopril (n=18), candesartan (n=20), or hydrochlorothiazide (n=15); 47 completed 6 months, and 31 completed 12 months. A sample description is provided in the eTable (http://www.archinternmed.com). The number of subjects achieving blood pressure control were similar (lisinopril, 91%; candesartan, 100%; and hydrochlorothiazide, 100%; $P=.40$) and systolic blood pressure reductions were similar in all 3 groups (mean [SD] reduction was 28 [5] mm Hg for lisinopril, 27 [5] mm Hg for candesartan, and 21 [5] mm Hg for hydrochlorothiazide; $P=.75$). There were no differences in the reported adverse events between the 3 groups. After adjusting for age and baseline MMSE score, those randomized to candesartan demonstrated the greatest improvement in TMT part B ($P=.008$); the adjusted TMT (parts A and B), which adjusts the test for motor speed ($P=.01$); and the recognition portion of the HVLT ($P=.03$) (**Figure**).

Comment. This study suggests that ARBs are associated with improvement in executive function in older hypertensive adults with early executive cognitive impair-

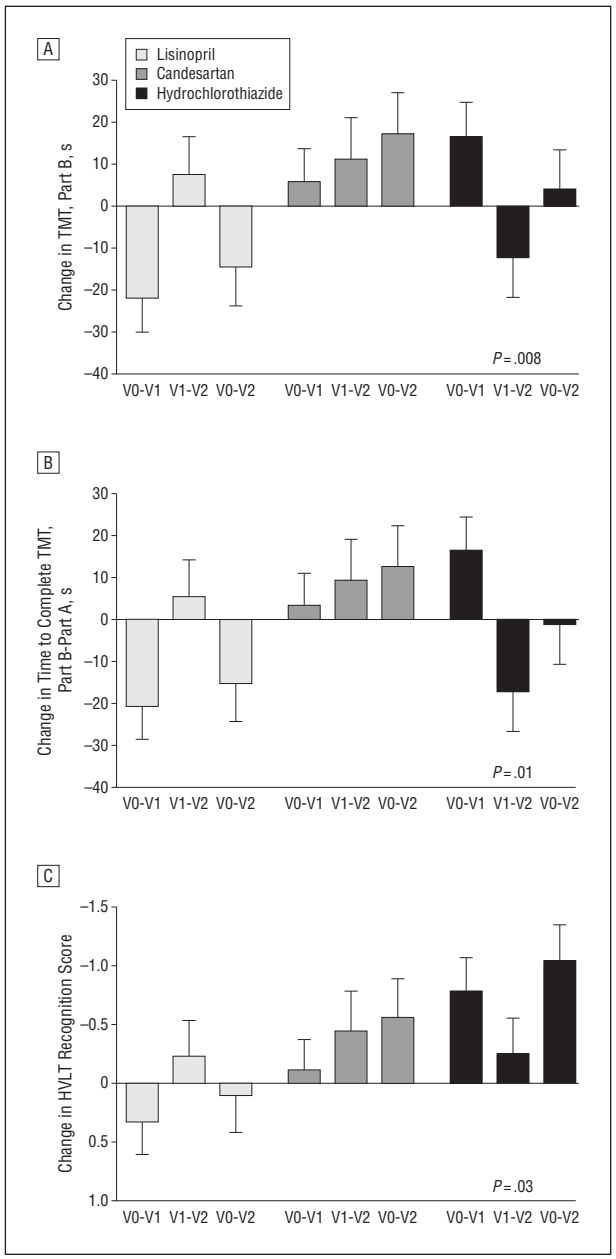

Figure. Significant changes in the adjusted least-square mean over study period in the 3 groups. A, Trail-Making Test (TMT), part B; B, Adjusted TMT (part A–part B); and C, Hopkins Verbal Learning Test–Revised (HVLT), recognition score. Least-square means were adjusted for age and baseline Mini-Mental State Examination. *P* values were obtained from the linear mixed model for the visit by group interaction parameter. V0-V1 indicates change from baseline to 6 months; V0-V2, change from baseline to 12 months; and V1-V2, change from 6 months to 12 months.

ment. To our knowledge, this is the first study to investigate the effect of antihypertensive therapy on executive function. Prior clinical trials that assessed cognitive outcomes of antihypertensive medications have excluded those with existing cognitive impairment and have used the MMSE, which is not sensitive to the domains related to frontal lobe executive dysfunction. Our findings further support observational data showing that ARB use is associated with lower risk of dementia and Alzheimer disease compared with the use of ACEIs or other antihypertensives.[6] The mechanisms of the potential superior effects of ARBs on cognition may be related to restoring proper central endothelial function, decreasing inflammation, and preventing neuronal degeneration through the selective noninhibition of the type 2 angiotensin receptors in the brain.[4,7,8] If confirmed in a larger trial, ARBs may be the optimal antihypertensive treatment for elderly patients with hypertension and cognitive impairment. Future large-scale studies exploring the effects of ARBs on cognitive impairment are needed.

Ihab Hajjar, MD, MS
Meaghan Hart, BSc
Yu-Ling Chen, MS
Wendy Mack, PhD, MS
William Milberg, PhD
Helena Chui, MD
Lewis Lipsitz, MD

Author Affiliations: Division of Geriatric, Hospital & General Internal Medicine, Department of Medicine (Dr Hajjar), Alzheimer Disease Research Center, Department of Neurology (Ms Chen), Department of Biostatistics (Dr Mack), and Department of Neurology, Raymond and Betty McCarron Chair in Neurology (Dr Chui), University of Southern California, Los Angeles; Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts (Ms Hart and Dr Lipsitz); Department of Psychiatry, Harvard Medical School, and New England Geriatric Research, Education and Clinical Center (GRECC), Boston Division, VA Boston Healthcare, Boston, Massachusetts (Dr Milberg); and Harvard School of Medicine and Division of Gerontology, Beth Israel Deaconess Medical Center, Boston (Dr Lipsitz).
Correspondence: Dr Hajjar, Department of Medicine, University of Southern California, 2020 Zonal Ave, IRD 320, Los Angeles, CA 90033 (ihajjar@usc.edu).
Author Contributions: *Study concept and design:* Hajjar, Milberg, and Lipsitz. *Acquisition of data:* Hajjar and Hart. *Analysis and interpretation of data:* Hajjar, Chen, Mack, Chui, and Lipsitz. *Drafting of the manuscript:* Hajjar, Mack, and Lipsitz. *Critical revision of the manuscript for important intellectual content:* Hajjar, Hart, Chen, Mack, Milberg, Chui, and Lipsitz. *Statistical analysis:* Hajjar, Chen, and Mack. *Obtained funding:* Hajjar and Lipsitz. *Administrative, technical, and material support:* Hajjar, Hart, and Lipsitz. *Study supervision:* Hajjar, and Mack, Milberg, Chui, Lipsitz.
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Total Daily Physical Activity and Longevity in Old Age

Increased levels of exercise are currently recommended to improve health and increase longevity, but gaps in our knowledge impede the formulation of evidence-based recommendations, particularly in older individuals.[1] Most studies of physical activity in old age have focused on self-reported physical activity measures, which are affected by recall bias. Moreover, few studies have examined the contribution of nonexercise physical activity to survival in old age.[2-4] We tested the hypothesis that an objective measure of total daily activity, including both exercise and nonexercise physical activity, is associated with longevity in community-dwelling older persons.

Methods. We used clinical data from participants of the Memory and Aging Project, a longitudinal cohort study of aging.[5] The study was approved by Rush University Medical Center institutional review board. Total daily physical activity (exercise and nonexercise physical activity) was measured at baseline for up to 10 days with actigraphs (Actical; Philips Healthcare) worn on the wrist 24 h/d.[6] All participants underwent structured annual clinical examination as previously described.[5]

Results. There were 893 participants, with a mean (SD) age of 82.0 (7.30) years and mean (SD) education of 14.8 (2.97) years; 76.3% were women; and 11.8% had clinical dementia. Total daily physical activity was measured for a mean (SD) of 9.3 (1.2) days. Total daily physical activity ranged from 0.06×10^5 counts/d to 13.56×10^5 counts/d (mean [SD]: 2.88×10^5 [1.57×10^5] counts/d).

During a mean follow-up of 4 years, there were 212 deaths (23.7% of cohort). In a Cox proportional hazards model adjusting for age, sex, and education, a higher level of total daily physical activity was associated with a decreased risk of death (hazard ratio [HR], 0.71; 95% CI, 0.63-0.79). Thus, an individual with high total daily physical activity (90th percentile) had approximately one-fourth the risk of death compared with an individual with low total daily physical activity (10th percentile).

In further sensitivity analyses, the association of total daily activity and death remained significant even after excluding (1) individuals with clinical dementia (HR, 0.77; 95% CI, 0.68-0.88); (2) cases with a history of stroke or Parkinson disease (HR, 0.73; 95% CI, 0.64-0.83); or (3) cases dying during the first 3 years of follow-up, leaving 79 incident cases of death (HR, 0.81; 95% CI, 0.68-0.97). Total daily physical activity was associated with death even after adjusting for several possible confounders including traditional self-reported physical activity and the frequency of other late-life social and cognitive activities, level of motor and cognitive function, chronic health conditions, and depressive symptoms alone (**Table**). The association between total daily activity and risk of death did not vary by age, sex, or education (results not shown). Al-

Table. Total Daily Physical Activity, Potential Confounders, and Risk of Death

Models	Terms Added to Core Model[a]	HR for Total Daily Physical Activity and Risk of Death
A	Late-life physical, social, and cognitive activity	0.77 (0.69-0.87)
B	Cognitive function	0.78 (0.69-0.88)
C	Motor function	0.85 (0.75-0.96)
D	Chronic health conditions	0.77 (0.68-0.88)
E	Depressive symptoms	0.74 (0.65-0.83)
F	Late-life physical, social, and cognitive activity, cognitive function, chronic health conditions, depressive symptoms	0.85 (0.75-0.97)

[a] A series of Cox proportional hazard models were examined to determine if potential confounders affected the association of total daily physical activity and the risk of death. *Core Model:* A Cox proportional hazard model was used to estimate the risk of death and included terms for age, sex, education, and total daily physical activity. *Physical Activity:* Self-reported frequency of participation in 5 physical activities (hours per week); a higher score indicates more frequent participation. *Social Activity:* Self-reported frequency of participation in 6 items about activities involving social interaction; a higher score indicates more frequent participation. *Cognitive Activity:* Self-reported frequency of participation in 7 cognitive activities; a higher score indicates more frequent participation. *Cognitive Function:* Composite measure of cognition based on performances on 19 cognitive tests; a higher score indicates a higher level of cognition. *Motor Function:* Composite measure summarizing 11 motor performance tests. *Chronic Health Conditions:* included linear and nonlinear terms for body mass index, as well as a term for the sum of 3 vascular risk factors (hypertension, diabetes, and smoking) and a term for the sum of 4 vascular diseases (myocardial infarction, congestive heart failure, claudication, and stroke). *Depressive Symptoms:* Modified 10-item Center for Epidemiologic Studies Depression scale; a higher score indicates more depressive symptoms.