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Original Study

Antihypertensive Medication Regimen Intensity and Incident Dementia in an Older Population

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A B S T R A C T

Objective: To investigate the association between antihypertensive medication regimen intensity and risk of incident dementia in an older population.
Design: Prospective, longitudinal cohort study.
Participants/Setting: A total of 1208 participants aged ≥78 years, free of dementia, and residing in central Stockholm at baseline (2001–2004).
Measurements: Participants were examined at 3- and 6-year follow-up to detect incident dementia. Data were collected through face-to-face interviews, clinical examinations, and laboratory tests. Data on antihypertensive use were obtained by a physician through patient self-report, visual inspection, or medical records. Cox proportional hazards models were used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between time-varying antihypertensive regimen intensity and incident dementia after adjusting for potential confounders.
Results: During the follow-up period, 125 participants were diagnosed with dementia. Participants who developed dementia were more likely to have vascular disease at baseline (66.4% vs 55.3%, $P = .02$). In fully adjusted analyses, the number of antihypertensive classes (HR 0.68, 95% CI 0.55–0.84) and total prescribed daily dose (HR 0.70, 95% CI 0.57–0.86) were significantly associated with reduced dementia risk. After considering all-cause mortality as a competing risk, the number (HR 0.75, 95% CI 0.62–0.91) and doses (HR 0.71, 95% CI 0.59–0.86) of antihypertensive classes, and the independent use of diuretics (HR 0.66, 95% CI 0.44–0.99), were significantly associated with lower dementia risk.
Conclusions: Greater intensity of antihypertensive drug use among older people may be associated with reduced incidence of dementia.
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Dementia is a major public health concern that affects over 44 million individuals worldwide.[1] Hypertension is associated with an increased risk of both vascular dementia and Alzheimer's disease.[2] However, studies on the association between antihypertensive use and reduced dementia risk have produced inconsistent findings.[3,4] A network meta-analysis of randomized trials and observational studies reported that antihypertensive treatment may reduce the risk of all-cause dementia by 9% [hazard ratio (HR) 0.91, 95% confidence interval (CI) 0.89–0.94].[5] In particular, the use of diuretics, calcium channel blockers, and renin-angiotensin system blocking agents have been found to be associated with reduced dementia risk.[6–8] However,

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methodological limitations of previous observational studies, including differing exposure and outcome measures, and short follow-up durations, hamper general conclusions.[3,9] Although it has been postulated that increased cerebral perfusion from antihypertensive withdrawal may help prevent cognitive decline, a recent Cochrane review reported that there is uncertain evidence in relation to withdrawing antihypertensive treatment to prevent cognitive decline or dementia.[10]

Cardiovascular disease, leading to cerebral ischemia, hypoperfusion, and hypoxia, has been associated with the development of dementia.[11] Some studies have suggested that the potential benefits of antihypertensive therapy on dementia incidence may extend beyond their blood pressure-lowering properties.[4] These additional neuroprotective and disease-modifying properties include potential attenuation of the development of amyloid beta pathology.[12,13]

Taken together, the potentially protective effects of antihypertensive medication regimens on dementia remain uncertain. In particular, the impact of antihypertensive medication regimen intensity (characterized by numbers and types of drug classes and doses used) remains unknown. The aim of this study was to investigate the association between antihypertensive medication regimen intensity and incident dementia in an older population.

Methods

Study Sample

Data were derived from the Swedish National study on Aging and Care in Kungsholmen (SNAC-K) population study. SNAC-K is an ongoing, longitudinal, population-based study of individuals aged ≥60 years living either at home or in institutions in Kungsholmen, a central area of Stockholm, Sweden, as previously reported.[14] In brief, the sample was randomly selected by specific age cohorts and different follow-up intervals. In this study, we examined participants from the older cohort (≥78 years old) who were followed up at 3 and 6 years so that all participants had an equal opportunity to be diagnosed with dementia. Baseline examination occurred between 2001 and 2004, with the first and the second follow-ups in 2004–2007 (3-year follow-up) and 2007–2010 (6-year follow-up), respectively.

There were 1581 participants in the older cohort at baseline. In the current analysis, participants were excluded for having prevalent dementia or questionable dementia at baseline (n = 293), for missing dementia status at baseline (n = 6), and for having no follow-up examination (n = 74). Compared with excluded participants, included participants were younger [baseline mean age (standard deviation) 84.1(5.6) vs 88.7 (6.4) years, $P < .01$], had fewer women (70.2% vs 83.1%, $P < .01$), and were better educated (for university education 20.0% vs 11.1%, $P < .01$).

Ethical Considerations

SNAC-K received ethical approval from the Ethics Committee at Karolinska Institutet and the Regional Ethics Review Board in Stockholm. This study was registered with the Monash University Human Research Ethics Committee. Written informed consent was obtained from all participants or from their proxies when participants were unable to provide informed consent.

Data Collection and Assessments

Data were collected by trained staff (nurses, physicians and psychologists) through face-to-face interviews, clinical examinations, and testing of participants at each visit. Dates of death for all participants were obtained from the death registry.

Assessment of Use of Antihypertensive Medications

Medication data were collected by a physician during clinical examination at baseline and follow-up. Participants were instructed to present a list of currently used medications, including both regular and as-required prescription and nonprescription medications. Current use was defined as use at the time of interview for regular medications, and use within the preceding month for as-required medications. Where available, physicians inspected prescriptions and medication containers to verify medication use. For participants who were institutionalized, medication information was extracted directly from the medical records.

All medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Antihypertensive treatments were defined as antiadrenergic agents and others (ATC code, C02), diuretics (C03), beta blockers (C07), calcium-channel blockers (C08), angiotensin-converting enzyme (ACE) inhibitors (C09A, C09B), and angiotensin receptor blockers (ARBs) (C09C, C09D). Treatment was classified as monotherapy or combination therapy if participants used 2 or more different antihypertensive drugs concurrently. Antihypertensive doses were expressed as prescribed daily dose (PDD)[ie, the proportion of defined daily dose (DDD) for the respective drug taken].[15] If more than 1 antihypertensive drug was used, their PDDs were summed. In fixed-dose combinations, each antihypertensive contained contributed separately to the PDD.

Diagnosis of Dementia

At each follow-up, dementia diagnosis was determined by the examining physicians according to the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* criteria, using a previously validated procedure.[14,16]

Covariates

Data on age, sex, and education were ascertained from the nurse interview at baseline. Education was defined by the maximum number of years of formal schooling and categorized as elementary school, high school and university. Arterial blood pressure was measured twice at a 5-minute interval on the right arm in a sitting position by trained nurses using a sphygmomanometer at baseline and follow-up, and the average of the 2 readings at each visit was used in the analysis.[17] History of cardiovascular diseases was ascertained by a physician based on clinical examination, electrocardiogram, self-reported medical history, or inpatient register information.[17] Diagnosis of cardiovascular diseases was made according to the *International Classification of Diseases, Ninth and Tenth Revisions* (ICD-9 and ICD-10) and included cardiac arrhythmia (ICD-9 code 427 and ICD-10 codes I48-I49), ischemic heart disease (ICD-9 codes 410-414 and ICD-10 codes I20-I25), heart failure (ICD-9 code 428 and ICD-10 code I50), and cerebrovascular disease (ICD-9 codes 436-438 and ICD-10 codes I60-I69). For the analysis, cardiovascular disease was defined as the presence of at least 1 cardiovascular disease. History of diabetes was defined based on self-reported medical history, inpatient register information (ICD-9 code 250 and ICD-10 codes E10-E14), use of antidiabetic agents (ATC code A10), or glycosylated hemoglobin (HbA1c) ≥6.5%. History of hypertension was defined as blood pressure ≥140/90 mmHg. History of dyslipidemia was defined as serum total cholesterol ≥6.22 mmol/L. Cognitive functioning at baseline was assessed with the Mini-Mental State Examination (MMSE).[18] Apolipoprotein E (APOE) allelic status was assessed according to a standard procedure, and categorized into any $\varepsilon 4$ present and absent.[19]

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