1.a. Full Title: Midlife use of renin-angiotensin antihypertensive medication, cognitive decline and late life dementia risk over 25-years: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Antihypertensives and dementia risk

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _WW_ [please confirm with your initials electronically or in writing]

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3. Timeline: We anticipate data will be received and cleaned in months 1-3, analyses will be completed in months 3-9, and manuscripts submitted within 1 year of proposal acceptance.

4. Rationale:
Alzheimer’s disease (AD) is a rapidly growing clinical and public health issue, primarily due to the increasing number of oldest old with currently no disease-modifying medications available for the treatment of AD. Thus, identifying new and potentially effective approaches to prevention and/or treatment is critical given the dearth of effective interventions to date.

Recent advances in research have demonstrated the presence of mixed rather than single brain pathologies in patients with dementia, with combinations of various forms of vascular disease and AD pathology (1,2). There is evidence that pathological changes in the brain precede
symptoms by years and furthermore, that vascular changes possibly precede AD pathology (3). There is mounting evidence that vascular risk factors, including hypertension (HTN), especially in mid-life are associated with increased AD risk in late life (4).

In recent years involvement of the renin angiotensin system (RAS) has been shown in AD pathogenesis. The RAS, which generates bioactive angiotensin peptides with a wide range of biological activities, plays a key role in blood pressure (BP) regulation and memory, and there is emerging evidence about its possible involvement in the pathogenesis of AD by BP control and/or other mechanisms, including vascular function, modulation of amyloid and tau metabolism, and inflammation (5-12).

Epidemiological studies evaluating late life antihypertensive medication (AHM) use suggest that medications acting via the RAS, such as angiotensin converting enzyme inhibitors (ACE-I) and angiotensin 1 receptor blockers (AT1RB), protect against cognitive decline, AD risk (13) and risk of MCI conversion to AD (14), and that repurposing these drugs may have therapeutic potential in AD. However, because the effects of cardiovascular disease during middle adulthood may be most critical to influencing later dementia risk, it is necessary to understand whether midlife use of AHM acting on the RAS pathway may influence later life neurocognitive outcomes. There are currently no studies evaluating effect from midlife use of AHM acting via the RAS (RAS-AHM) on late life AD risk.

The goal of our proposed study is to evaluate the effect of midlife use of RAS-AHM on cognitive function and dementia risk when compared to other-AHM users (including calcium channel blocker, diuretic and beta blocker users) and non-users in ARIC Study participants.

5. Main Hypothesis/Study Questions:

Based on previous research, we hypothesize that the use of RAS-AHM medications in midlife is associated with decreased cognitive decline and incident all-cause dementia when compared to other-AHM or non-AHM users.

Our long-term goal is to identify medication groups that may modify dementia risk, and to better understand the mechanisms by which these medication groups affect AD pathways. Based on these hypothesis and goals, the specific aims of these proposed analyses are:

Hypothesis 1: We hypothesize that the use of RAS-AHM in midlife is associated with less incident all-cause dementia when compared to other-AHM or non-AHM users.

To address hypothesis SA1: We will determine whether RAS-AHM use in middle age is associated with incident all-cause dementia over a 25-year follow-up period, when compared to other-AHM or non-AHM users in all participants.

Hypothesis 2: We hypothesize that the use of RAS-AHM in midlife is associated with less decline in global cognition and DSST when compared to other-AHM or non-AHM users.

To address hypothesis SA2: We will determine whether RAS-AHM use is associated with steeper cognitive decline, on a global cognitive measure and the digit symbol substitution test (DSST), over a >25-year follow-up period, when compared to other-AHM users or non-AHM users in all participants.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).
Study design: Prospective cohort study.
Participants: We will use data of all participants, however to evaluate the role of hypertension in a sensitivity analysis we will only include participants with history of hypertension.

Measures of medication use:
Participants reporting use of ACE-I or ATR1B use at least at 2 or more non-consecutive visits during the first 10 years of the study will be coded as RAS-AHM users, while participants reporting use at 2 or more non-consecutive visits during the first 9 years of the study (Visits 1, 2, 3 and 4) of beta blockers (BB), calcium channel blockers (CCB), diuretics will be coded as other-AHM users. To maintain adequate sample size and statistical power, similar to previous studies we will allow participants to switch medication group over the whole study period, which may result in some participants being assigned to both groups. However, we will perform sensitivity analysis where we only will include participants taking RAS-AHM or other-AHM across all the visits, while participants assigned to both AHM medication user groups will be excluded.

In a sub-analysis RAS medication use will be further stratified by blood-brain barrier penetrance of RAS-AHM and by blood pressure control status.

Outcome measures:
1. Incidence of all-cause dementia, since it is available for the whole cohort and defined as a combination of the following: adjudicated dementia diagnoses at visits 5 or 6; hospitalization codes for dementia; scoring low on the TICS for people unwilling to come in; having a telephone informant interview (for people unwilling or unable to be tested or deceased) using the SIS and the AD8 c/w dementia. (level 3 dementia)
2. Global cognitive function (average of DSST, WFT, and DWRT), and separate cognitive scores for DSST at visits 2, 4 and 5, and 6.

Confounding variables:
- Demographic and Psychosocial Variables: age, sex, race, center, education.
- Comorbid diseases (from visit 1 for dementia analyses, and from visit 2 for cognitive change analysis): diabetes mellitus (DM), hyperlipidemia, renal disease, coronary heart disease (CHD), atrial fibrillation, stroke; and depression using CES-D measure at visits 5 and 6.
- Vascular risk factors: mean systolic and diastolic blood pressure during whole study, cholesterol levels, glucose levels and HgbA1C levels.
- Risks for adverse health outcomes: cigarette smoking status (visit 1 for dementia analyses; visit 2 for cognitive change analyses), physical activity (Baecke physical activity questionnaire; from visit 1), alcohol use (v1/ v2 as above) and measures of BMI (v1/ v2 as above), APOE ε4 genotype.
- Medication: dementia medication

Methods for handling confidentiality:
Analyses will be conducted entirely on data already collected under the ARIC protocol, which is deidentified. Data obtained during the study will be kept confidential and in password-protected electronic files, with access limited to study personnel only. Individual participants will not be identifiable in reports/manuscripts because all patient identifiers are removed prior to investigator access to data.
Data Analysis Plan:
First, information on age, sex, race-center, education, comorbidities, cigarette smoking, alcohol use, physical activity, BMI, Apo ε4 and the use of AHM (RAS-AHM, other-AHM and non-AHM at baseline and over follow-up period (visit 1-6) will be analyzed.
We will compare baseline characteristics between RAS-AHM and other-AHM or non-AHM user groups by using Chi-square tests for categorical variables and t-test for continuous variables by using SAS version 9.1 (SAS Institute Inc., Cary, NC) with the a priori p-value of p<0.05.

Hypothesis 1: We hypothesize that the use of RAS-AHM in midlife is associated with less incident all-cause dementia when compared to other-AHM or non-AHM users.

To address hypothesis SA1: We will determine whether RAS-AHM use in middle age is associated with incident all-cause dementia over a 25-year follow-up period, when compared to other-AHM or non-AHM users in all participants.

We will evaluate associations between RAS-AHM use in mid-life and incident all-cause dementia over a 25-year follow-up period, when compared to other-AHM or non-AHM users in all participants.

We will be using Cox proportional hazard models with time-dependent covariates. Analyses will be adjusted for potential confounding effects of age, sex, education, race-center, smoking, alcohol use, BMI, depression, Apoε4 status, mean systolic and diastolic blood pressure at time of reported AHM use, diabetes mellitus, hyperlipidemia, history of CHD/stroke/atrial fibrillation, cholesterol levels, HgbA1C levels. We will estimate risk for incident all-cause dementia over a 25-year interval among RAS-AHM users when compared to other-AHM or non-AHM users.

The following sensitivity analyses will be performed: 1) to assess role of history of hypertension, we will only include participants with history of hypertension, 2) to assess the role of incidence of stroke during the study period, we will exclude participants with incident stroke before dementia diagnosis, and 3) we will be applying a 6-month lag, where information on reported medication use proximal to the time of diagnosis of impairment will be ignored, because it may have represented a prodromal treatment effect.

To indication bias issues, we will perform a separate analysis in participants with no history of hypertension, which we will be able to do since RAS-AHM are indicated for congestive heart failure, heart attack and in diabetes mellitus.

Hypothesis 2: We hypothesize that the use of RAS-AHM in midlife is associated with less decline in global cognition and DSST when compared to other-AHM or non-AHM users.

To address hypothesis SA2: We will determine whether RAS-AHM use in mid-life is associated with steeper cognitive decline, on a global cognitive measure and the digit symbol substitution test (DSST), over a >25-year follow-up period, when compared to other-AHM users or non-AHM users in all participants.

We will evaluate cognitive change over a >25-year interval (visit 2 through visit 6) among participants reporting RAS-AHM use in mid-life when compared to other-AHM or non-AHM users. We will use cognitive scores for the DSST, WFT, and DWRT obtained during visits 2, 4, 5, and 6 which were transformed at each visit to Z scores. Scores will be standardized by
subtracting test scores of each visit from mean score at visit 2 and dividing it by SD of visit 2 scores.

We will be using Generalized Estimation Equation (GEE) with unstructured correlation matrix and robust variation. The GEE contains linear spline terms representing the time in years since the Visit 2 cognitive testing baseline, with a knot 6 years post Visit 2 as is standard in ARIC analyses (due to the long interval between Visits 4 and 5). Analyses will be adjusted for potential confounding effects of age, sex, education, race-center, smoking, alcohol use, BMI, depression, Apoϵ4 status, mean systolic and diastolic blood pressure at time of reported AHM use, diabetes mellitus, hyperlipidemia, history of CHD/stroke/atrial fibrillation, cholesterol levels, glucose levels, HgbA1C levels and also dementia medications used.

We will evaluate the effect of the timing of medication use on cognitive change between visits 4 and 6, for which we will use time-AHM spline term with a knot at the visit prior to the first reported AHM use. We will use marginal construction of the post-knot spline term to compare change in slope between prior or AHM initiation.

The following sensitivity analyses will be performed: 1) to assess role of history of hypertension, we will only include participants with history of hypertension, 2) to assess the role of incidence of stroke during the study period, we will exclude participants with incident stroke and 3) to assess role of missing cognitive testing we will use multiple imputations with chained equations (MICE), which has previously been validated in ARIC (15). We will be using baseline (Visit 2) cognitive scores and participant covariates detailed above to impute missing cognitive data and missing covariates from Visits 4, 5, and 6.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _X___ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? ____ Yes _X__ No

(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? _X__ Yes ____ No

APOE genotype will be used.

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”? _X__ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

_____ x__ Yes _______ No
10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)? – There was one manuscript published (see below) evaluating cross-sectionally associations between aspirin use and cognitive function in midlife. There were no published or unpublished proposals evaluating longitudinally antihypertensive medication use and dementia risk/cognitive function.


11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ yes  ____ No (ARIC-Neurocognitive Study)

11.b. If yes, is the proposal
___ X__ A. primarily the result of an ancillary study (list number* _2008.06 ___)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at https://www2.cscc.unc.edu/aric/approved-ancillary-studies

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PubMed Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.csec.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

References:


