ARIC Manuscript Proposal #3166

PC Reviewed: 5/8/2018 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Association of hypertension according to new ACC/AHA blood pressure guidelines with incident dementia in the ARIC cohort.

b. Abbreviated Title (Length 26 characters): **New hypertension categories and dementia**

2. Writing Group: Jeffrey Hodis, Rebecca Gottesman, B. Gwen Windham, David Knopman, Pamela Lutsey, Alvaro Alonso

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

First author: Jeffrey Hodis
Address: 1659 Briarcliff Rd NE
Atlanta, GA 30306

Phone: (626) 807-3941 Fax: N/A
E-mail: jeffrey.daniel.hodis@emory.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: Alvaro Alonso, MD, PhD
Address: Emory University Rollins School of Public Health
1518 Clifton Rd NE
Atlanta, GA 30322

Phone: (404) 727-8714 Fax: (404) 727-8737
E-mail: alvaro.alonso@emory.edu

3. Timeline: completion by May 2019

4. Rationale: Studies from the ARIC-NCS have established associations between cardiovascular risk factors, primarily midlife hypertension and diabetes, and the development of dementia and cognitive decline.[1,2] However, in 2017, the American College of Cardiology (ACC) and the American Heart Association (AHA) changed the definition of high blood pressure, lowering the cutoff to define hypertension. This announcement marks the first comprehensive change to the categorization of hypertension since 2003 and is now estimated to

include about 46% of the U.S. adult population as having hypertension.[3] The most significant change is the removal of the prehypertension classification, instead classifying people as having normal blood pressure, elevated blood pressure, stage 1 hypertension, and stage 2 hypertension.

Previous studies examining the association of hypertension with dementia risk conducted on ARIC-NCS and other cohorts were based on the old guidelines, leaving unanswered questions as to how the new levels of hypertension relate to the development of dementia. Using data from the 5 visits and dementia surveillance in the ARIC study, we propose conducting an analysis examining the relationship of dementia with blood pressure categories using the updated hypertension guidelines. This study will estimate the association of blood pressure levels according to categories defined in the 2017 ACC/AHA guidelines with the risk of dementia, overall and stratified by sex and race (white vs. African American). In addition, we will calculate the population attributable fraction of dementia associated with the new categories and compare it to the population attributable fraction corresponding to hypertension defined according to the older guidelines.

5. Main Hypothesis/Study Questions:

1. Specific Aim 1: To assess the association of hypertension and of BP categories defined according to the ACC/AHA guidelines with the risk of incident dementia
    a. We hypothesize that midlife hypertension, as defined by the new guidelines, is related to increased risk of incident dementia (especially among the African American population). The association of hypertension stage 2 with dementia will be stronger than for hypertension stage 1 (compared to normal blood pressure).
2. Specific Aim 2: To calculate the population attributable fractions of hypertension and of BP categories defined according to the ACC/AHA guidelines with the risk of incident dementia.
    a. We hypothesize that hypertension will be responsible for a large proportion of dementia cases in this population, as defined by the population attributable fraction. Population attributable fraction with the new definition will be only modestly larger than with the old hypertension definition.

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

The study will examine all ARIC participants without dementia at baseline and with information on blood pressure and other covariates at the baseline visit. Participants who are not identified as African American or white will be excluded, in addition to the small African American population from the Maryland and Minnesota centers (due to issues with adjusting for race and center that would arise when the two populations in question are substantially different in size).

Main exposure

The primary exposure is hypertension defined according to the new ACC/AHA guidelines [systolic blood pressure (SBP) ≥130 or diastolic blood pressure (DBP) ≥80]. We will also

categorize individuals according to blood pressure categories [normal BP (SBP 120-129 and DBP <80), hypertension stage 1 (SBP 130-139 or DBP 80-89), hypertension stage 2 (SBP ≥140 or DBP ≥90)]. Participants using antihypertensive medication will be considered in the hypertension stage 2 group.

We will also categorize participants according to the JNC7 guidelines [hypertension if SBP ≥140 or DBP ≥90; BP categories: normal (SBP <120 and DBP <80, prehypertension (SBP 120-139 or DBP 80-90, hypertension stage 1 (SBP 140-159 or DBP 90-99, hypertension stage 2 (SBP ≥160 or ≥100)].

Main outcome variable: incident dementia

This analysis will use incident dementia as the primary outcome. Dementia will be defined using adjudicated dementia diagnoses at visit 5, informant telephone interview, and ICD-9 codes from hospitalizations and death certificates along with classification of cognitive status based on standardized definitions of dementia.[2,6]

Covariates

Covariates that will be considered as potential confounders include race and study site, sex, age, education level, apoE genotype status, smoking, alcohol consumption, physical activity, hyperlipidemia, diabetes, and BMI. Separate models will additionally adjust for prior history of coronary heart disease, stroke or heart failure.

Statistical analysis

We will use Cox proportional hazards regression models to estimate hazard ratios and 95% confidence intervals of dementia by hypertension categories, adjusting for potential confounders. The primary endpoint will be time between visit 1 and diagnosis of dementia, lost to follow-up or administrative censoring, whichever comes first. Initial models will adjust for age, sex, race-site and education. A second model will include potential confounders (listed above), with a final model adjusting for additional variables that could be considered confounders or mediators (e.g. history of CVD). WE will conduct additional analyses stratifying by sex and race. We will repeat these analyses using the 2017 ACC/AHA guidelines categories and the JNC7 categories. Depending on the degree of missingness for the exposure and covariates, we will consider using multiple imputation approaches.

We will calculate population attributable fractions of dementia by categories of hypertension using standard approaches. Specifically, we will calculate rate ratios using Poisson regression and applying previously described formulas that take into account the prevalence of the risk factor in the populations.[4,5] This will be done separately for both 2017 ACC/AHA and JNC7 categories.

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? _X_ Yes ____ 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

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/search.php

___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)?

2120C Incidence of dementia and its relationship to midlife vascular risk factors in ARIC (Gottesman)
2175 Midlife blood pressure and 20-year cognitive change (Gottesman)
3069 Blood pressure trajectories from midlife to late life and cognitive change (Yano)

None of the previously approved manuscripts specifically address the association of the new hypertension categories with dementia. Rebecca Gottesman, who has led some of this work, is included as a coauthor in this proposal and has approved it.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal

_X_ A. primarily the result of an ancillary study (list number* 2008.6)
___ 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 http://www.cscc.unc.edu/aric/forms/

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.cscc.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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript __ Yes _X__ No.

1. Gottesman RF, Schneider AL, Albert M, et al. Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. *JAMA Neurol.* 2014;71(10):1218-1227.
2. Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incidence dementia in the atherosclerosis risk in communities (ARIC) cohort. *JAMA Neurol.* 2017;74(10):1246-1254.
3. "New ACC/AHA High Blood Pressure Guidelines Lower Definition of Hypertension." *American College of Cardiology*, 13 Nov. 2017, www.acc.org/latest-in cardiology/articles/2017/11/08/11/47/mon-5pm-bp-guideline-aha-2017.
4. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *American Journal of Public Health*. 1998;88:15-9.
5. Huxley RR, Lopez FL, Folsom AR, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the atherosclerosis risk in communities (ARIC) Study. *Circulation*. 2011;123(14):1501-1508.
6. Knopman DS, Gottesman RF, Sharrett AR, et al. Mild cognitive impairment and dementia prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study. *Alzheimer's & Dementia : Diagnosis, Assessment & Disease Monitoring*. 2016;2:1-11.