ARIC Manuscript Proposal #4456

PC Reviewed: 05/14/24 **Status: _____** **Priority: 2**

1.a. Full Title: Assessment of Associations between Hypertension Categories and Sex Specific Treatment Thresholds and All-Cause Mortality Events from the Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 58 characters): Sex-specific hypertension treatment thresholds and outcomes in ARIC

2. Writing Group:
Writing group members: Katie Williams, Stephen Juraschek (note this was discussed with Morgan Grams and Joe Coresh, who are interested, but have not reviewed yet), others welcome

Note this proposal is related to Dr. Juraschek's orthostatic hypotension and home blood pressure R01s.

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

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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).

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3. Timeline: Data analysis will begin once this proposal is approved with the goal of a abstract by May 2024 and manuscript draft by Fall 2024.

4. Rationale:

Hypertension is one of the most prevalent risk factors contributing to the development of cardiovascular disease, the leading cause of death in the United States. From age 30-65 years old, there is on average a 20 mmHg and 10 mmHg increase in systolic and diastolic blood pressure, respectively.[1] Hypertension is thought to increase risk of a major atherosclerotic cardiovascular disease outcome 2- to 3-fold.[2] In addition, the National Health and Nutrition Examination Survey (NHANES) suggests that 45.6% of the US population has hypertension.[3] This statistic has been largely stagnant the past five decades, therefore there is great potential for improved health through control of blood pressure.

Historically, a systolic blood pressure (SBP) of 120 mm Hg has been considered the upper limit of normal for adult systolic blood pressure. This threshold has served as an important target for treatment and cardiovascular event prevention. According to the 2017 American Heart Association (AHA) and American College of Cardiology (ACC) guidelines, subjects with a systolic blood pressure of 120-129 mm Hg and diastolic pressure of <80 mm Hg are categorized as having an elevated blood pressure.[4] Another well-established clinical practice guideline by the European Society of Hypertension (ESH) cites systolic pressures of 130-139 mmHg and diastolic pressures of 85-89 mmHg as high-normal.[5] Both bodies set the BP target for treatment to be <130/80 mmHg. Epidemiologic evidence has consistently demonstrated a positive association between both systolic and diastolic blood pressures (DBP) and cardiovascular disease outcomes.[2,6,7]

Although there is a continuum of cardiovascular risk associated with varying levels of blood pressure, there is a lack of information regarding the absolute and relative risks of cardiovascular disease among these individuals. Moreover, there is limited data on potential sex differences. It is known that healthy women tend to have lower blood pressures than healthy men over the life course.[8] Yet, women begin to experience steeper increases in blood pressure beginning in their mid-30s and are more likely to have hypertension than men at ≥ 65 years old.[9] Additionally, a 2022 statement from the European Society of Cardiology and recent literature indicated that risk for cardiovascular events begins at different blood pressure categories in women versus men.[9–14] However, due to lack of specifically designed clinical trials, it is not known if hypertension should be differently managed in females and males, including treatment goals and choice and dosages of antihypertensive drugs.

In order to better inform this question, in this proposal we examine the relationship between blood pressure measured in men and women with respect to their distributions, risk factor burden, absolute risk, and relative risk of cardiovascular disease events. In addition we examine the relationship between blood pressure among treated adults with respect to both cardiovascular disease events and adverse events related to lower blood pressure (e.g., falls and sycope).

5. Main Hypothesis/Study Questions:

1. Hypothesis 1: The distribution of blood pressure will be greater among men compared with women.
2. Hypothesis 2: Cardiovascular risk factors will be more prevalent at lower blood pressure levels among women compared to men.

3. Hypothesis 3: Lower BPs among women will be associated with a higher relative risk of CVD events, but a lower absolute risk of CVD events compared to men.
4. Hypothesis 4: Women with low BPs in the context of hypertension treatment will not have a higher risk of adverse events (syncope, falls) than men, suggesting that more intensive treatment in women is safe.

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 with visit 1 as baseline.

Exclusions:

- ARIC participants with known prior CVD
- Missing covariates of interest (listed below)
- Persons of ethnicities other than African American or white
- African Americans from Washington County or Minnesota
- No prior history of falls, syncope, CVD or stroke.

Exposure assessment:
Seated blood pressures were measured during ARIC visit 1 (1987-1989) in over 10,060 ARIC participants. We will focus on visit 1 data (the largest visit with the longest follow-up time and lowest prevalence of hypertension treatment).

Primary outcomes: CVD, Stroke, Falls, Syncope, and Mortality
The primary outcomes in this study are (1) incident CVD (and its subtypes), (2) stroke, (3) falls, (4) syncope, and (5) mortality, after visit 1 through December 31, 2019. Falls and syncope will be defined as the first occurrence of any related hospitalization or claim for inpatient or outpatient services after the baseline visit. These outcomes were identified via two sources: 1) active surveillance of all hospitalizations for all ARIC participants; and 2) linkage to Centers for Medicare and Medicaid Services (CMS) claims data from 1991-2013.[18,19] For CVD, we will use the variables "C7_IN_19SP," "C7_IN19DP," and "C7_INCHF19." For mortality, we will use the variable "DEAD19."

The ARIC Study obtains hospitalization information from annual telephone contact with study participants and through surveillance of hospitals in the study communities (inpatient hospitalization data currently available from January 1st, 1988, through December 31, 2015). In the original ARIC protocol, surveillance was primarily focused on coronary heart disease, myocardial infarction, stroke, and heart failure outcomes, but thereafter included other diagnostic codes for hospitalized events, including those attributed to fall and syncope.

Participant data were also linked to CMS claims data using a finder file that included participants' social security numbers, sex, and date of birth through a matching process described previously.[18,19] These claims were available for eligible persons derived from two forms of coverage: (1) fee-for-service (FFS) or (2) managed care organizations. CMS data included inpatient and outpatient claims for participants enrolled in FFS continuously after reaching CMS

Medicare eligibility and those with intermittent FFS enrollment during the period of observation. While no outpatient claims were available for cohort participants enrolled in managed care programs, inpatient claims were available for all participants with Medicare on a selective basis from the year 2008 onward.

MedPar files were used to identify inpatient CMS records for hospital encounters related to falls, fractures, syncope, and motor vehicle accidents. Outpatient falls and motor vehicle accidents were identified using the Clinical Classification System (CCS) category 2603, E codes, which were based on International Classification of Diseases, 9th revision (ICD-9) external cause of injury codes. Falls were identified using the following ICD9 codes: E880.X-E888.X. Syncope was defined by ICD9 code: 780.2.

Blood Pressure Categories:
Systolic blood pressure will be categorized categories divided as follows:

- SBP <110 mm Hg
- SBP 110- <120 mm Hg
- SBP 120- <130 mm Hg
- SBP 130- <140 mm Hg
- SBP 140- <150 mm Hg
- SBP ≥ 150 mmHg

Other variables of interest:

Models will be adjusted for age, sex, race-center, non-race adjusted estimated glomerular filtration rate, body mass index, resting heart rate, high density lipoprotein cholesterol, total cholesterol, cholesterol lowering medications, hypertension lowering medications, leisure activity, diabetes, alcohol use, education, smoking status, prior stroke.

Data analysis:

Our primary analyses will be as follows:

- Baseline characteristics by sex and treatment status (**Table**), restricted to adults without prior CHD, CHF, or stroke
- Blood Pressure Percentiles for men and women, systolic and diastolic blood pressure (**Table**)
- Risk factors by systolic blood pressure categories (**Table**):
    - Mean body mass index, fasting glucose, LDL cholesterol, estimated glomerular filtration rate
    - Proportions of obesity, diabetes, dyslipidemia, CKD stage 3
    - PREVENT 10yr and 30yr risk
- Absolute risk by SBP categories for: coronary heart disease, CHF, stroke, and death (Table; cumulative incidence function **Figure**)
- Unadjusted and age/race adjusted linear regression of SBP by sex (**Figure** with Lowess and linear fit)
- Relative risk of CHD, CHF, stroke, and death using Cox proportional hazards models by SBP categories adjusted for the covariates above (**Table, Figure** restricted cubic spline)

- SBP categories and absolute/relative risk of syncope, fall, CHD, CHF, stroke, and death among treated men and women (**Table**)
- Conversion **Table** (combines comparison above in a translational fashion): men to women and women to men: SBP category thresholds for men or women and their equivalent value based on percentile, linear regression, risk factor burden, absolute risk, and relative risk
- Sensitivity analysis: repeat the above for DBP

Limitations:

- Insensitive event ascertainment (falls)
- Residual confounding is always a concern with observational studies.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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? ____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ 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/aricproposals/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)?

2023

Yeo WJ, Surapaneni A, Coresh J, Ballew S, Ozkan B, Schlosser P, Grams M. Sex differences in the risk of uncontrolled hypertension: Variation over the life course. ARIC Manuscript Proposal #4259.

Wang MC, Petito LC, Pool LR, et al. The 2017 American College of Cardiology/American Heart Association Hypertension Guideline and Blood Pressure in Older Adults. *Am J Prev Med*. 2023;65(4):640-648. doi:10.1016/j.amepre.2023.04.011

2021
Foti K, Matsushita K, Koton S, et al. Changes in Hypertension Control in a Community-Based Population of Older Adults, 2011-2013 to 2016-2017. *Am J Hypertens*. 2021;34(6):591-599. doi:10.1093/ajh/hpaa206

2020
McEvoy JW, Daya N, Rahman F, et al. Association of Isolated Diastolic Hypertension as Defined by the 2017 ACC/AHA Blood Pressure Guideline With Incident Cardiovascular Outcomes. *JAMA*. 2020;323(4):329-338. doi:10.1001/jama.2019.21402

Teramoto K, Nadruz Junior W, Matsushita K, et al. Mid- to Late-Life Time-Averaged Cumulative Blood Pressure and Late-Life Cardiac Structure, Function, and Heart Failure. *Hypertension*. 2020;76(3):808-818. doi:10.1161/HYPERTENSIONAHA.120.14833

2019
Rattani A, Claxton JS, Ali MK, Chen LY, Soliman EZ, Alvaro A. Association and impact of hypertension defined using the 2017 AHA/ACC guidelines on the risk of atrial fibrillation in The Atherosclerosis Risk in Communities study. *BMC Cardiovasc Disord*. 2019;19(1):262. Published 2019 Nov 26. doi:10.1186/s12872-019-1259-0

2016
Petruski-Ivleva N, Viera AJ, Shimbo D, et al. Longitudinal Patterns of Change in Systolic Blood Pressure and Incidence of Cardiovascular Disease: The Atherosclerosis Risk in Communities Study. *Hypertension*. 2016;67(6):1150-1156. doi:10.1161/HYPERTENSIONAHA.115.06769

2014
Rodriguez CJ, Swett K, Agarwal SK, et al. Systolic blood pressure levels among adults with hypertension and incident cardiovascular events: the atherosclerosis risk in communities study [published correction appears in JAMA Intern Med. 2014 Aug;174(8):1419]. *JAMA Intern Med*. 2014;174(8):1252-1261. doi:10.1001/jamainternmed.2014.2482

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)
___ 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 https://sites.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.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.

References

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2. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA*. 1996;275(20):1571-1576.

3. Muntner P, Carey RM, Gidding S, et al. Potential US Population Impact of the 2017 ACC/AHA High Blood Pressure Guideline. *Circulation*. 2018;137(2):109-118. doi:10.1161/CIRCULATIONAHA.117.032582

4. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71(6):e13-e115. doi:10.1161/HYP.0000000000000065

5. 2023 ESH Hypertension Guideline Update: Bringing Us Closer Together Across the Pond. American College of Cardiology. Accessed March 30, 2024. https://www.acc.org/Latest-in-Cardiology/Articles/2024/02/05/11/43/http%3a%2f%2fwww.acc.org%2fLatest-in-Cardiology%2fArticles%2f2024%2f02%2f05%2f11%2f43%2f2023-ESH-Hypertension-Guideline-Update

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16. Tinetti ME, Han L, Lee DSH, et al. Antihypertensive Medications and Serious Fall Injuries in a Nationally Representative Sample of Older Adults. *JAMA Intern Med*. 2014;174(4):588-595. doi:10.1001/jamainternmed.2013.14764

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19. Kucharska-Newton AM, Heiss G, Ni H, et al. Identification of Heart Failure Events in Medicare Claims: The Atherosclerosis Risk in Communities (ARIC) Study. *J Card Fail*. 2016;22(1):48-55. doi:10.1016/j.cardfail.2015.07.013