

ARIC Manuscript Proposal # 3124

PC Reviewed: 03/20/2018

Status: _____

Priority: 2

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title: Association and impact of hypertension defined using the new guidelines with risk of atrial fibrillation in the ARIC cohort.

b. Abbreviated Title (Length 26 characters):

2. Writing Group:

Writing group members: Anas Rattani, Mohammad Ali, Lin Y. Chen, Elsayed Z. Soliman, Alvaro Alonso

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AR_ **[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:

A draft will be ready for submissions for the Publications Committee Review in late spring of 2018

4. Rationale:

Atrial Fibrillation (AF) is a common chronic arrhythmia, occurring in 2.3 adult in the United States. Most of the population that develop AF are over the age of 65 with higher rates

among men than women and among whites than blacks (6). It is projected that by the year 2050, the prevalence of AF will increase by 2.5-fold because of a growing elderly population (4,5). This increase in the number of individuals with AF will also impact the burden of stroke, heart failure, and other heart problems in the population. For example, the prevalence of stroke is 30% among AF patients between 80-89 years old (14). Common risk factors for AF are obesity, diabetes, smoking, heavy drinking and hypertension. Amongst the risk factors listed, hypertension has the largest population attributable fraction for AF incidence and plays a major role in the management and prognosis of AF (8,12). Hypertension is very common among individuals with AF. Individuals with hypertension usually also have AF. For example, a study conducted in Germany found that atrial hypertension was the most common co-existing condition among AF patients. Sixty-nine percent of patients had hypertension compared to other conditions (11). In other studies, up to 90% of patients with AF are hypertensive (8). People with hypertension also have 1.7-fold higher risk of developing AF. One in six cases of AF is due to hypertension (3). Thus, early detection and management of hypertension is very important to prevent and manage AF.

Previous guidelines released by the Eighth Joint National Committee defined hypertension as a systolic blood pressure (SBP) ≥ 140 or diastolic blood pressure (DBP) ≥ 90 mmHg regardless of age. Blood pressure was divided into the following ranges: Normal = $< 120/80$, Prehypertension = $120-139/80-89$, Stage 1 hypertension = $140-159/90-99$, Stage 2 hypertension = $> 160/100$ (2). However, the American Heart Association/American College of Cardiology have released new guidelines last fall, lowering the threshold to define elevated blood pressure and thus impacting the number of individuals diagnosed with hypertension. The new recommended blood pressure range is divided into the following categories: Normal $< 120/80$, Prehypertension $120-129/80$, Stage 1 hypertension $130-139/80-89$, Stage 2 hypertension $\geq 140/90$ (1,9). This change means more individuals will be diagnosed with hypertension. However, it is uncertain whether individuals labeled as hypertensives with the new guidelines are at similarly increased risk of AF.

The goal of this proposal is to understand the association between hypertension and risk of AF using the diagnostic categories in the new guidelines, and evaluate the population attributable fraction of newly defined hypertension. Results from these analyses will contribute to inform the ideal blood pressure range for people with hypertension and risk of AF. Additionally, the study will help us estimate the potential population impact of preventing hypertension under the new guidelines.

5. Main Hypothesis/Study Questions:

Question: What is the risk of AF associated with hypertension based on the 2017 ACC/AHA hypertension guidelines compared to the old guidelines? What is the population attributable fraction of AF associated with hypertension according to the new guidelines?

Hypothesis: The establishment of the 2017 ACC/AHA hypertension guidelines will increase the number of people at risk for AF. Risk of AF in those newly labeled as hypertensives (stage 1, $130-139/80-89$) will be higher than among normotensives but lower than among those with stage 2 hypertension ($\geq 140/\geq 90$). The population attributable fraction of stage 1 will be small.

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

Inclusion/Exclusion criteria:

- Inclusion:
 - ARIC participants with baseline blood pressure readings.
- Exclusion:
 - Non-whites and non-blacks. Non-whites from the Minneapolis and Washington County centers.
 - Prevalent AF at baseline or missing ECG
 - Prevalent diabetes, coronary heart disease, stroke or heart failure
 - eGFR<60 ml/min/1.73 m²

Dependent Variable: Incident of AF through the end of 2015.

Independent Variable: Blood pressure categories divided into the ranged indicated in the old and new hypertension guidelines. Old: $\geq 140/\geq 90$. New: stage 1 130-139/80-89, stage 2 $\geq 140/\geq 90$. Participants using antihypertensive medication will be labeled as stage 2 independently of their visit blood pressure measurements

AF ascertainment: As previously described, using study ECGs, hospital discharge diagnoses, and death certificates (13).

Covariates: Sex, race, education, study center, height, body mass index (BMI), smoking status, alcohol usage.

Analysis: Analysis will be conducted using SAS 9.4 statistical software. Cox proportional models will be used to estimate hazard ratios of AF among individuals with hypertension based on the old and new guidelines. We will perform stratified analyses by sex and race to explore effect modification.

We will calculate population-attributable fractions (PAFs) to determine the possible impact of preventing hypertension on AF occurrence. PAFs will be computed according to the following formula (11): $PAF = p_i [(RR_i - 1) / RR_i]$, where p_i is the proportion of cases falling into i th exposure level and RR_i is the relative risk comparing i th exposure level with unexposed group ($i=0$). We will use Poisson models to obtain the RR.

Limitations: Hypertension, diabetes and obesity are all related. Someone who has hypertension tends also have diabetes or is obese. However, in this study we will be excluding persons with diabetes and adjusting for obesity, which will limit issues of confounding.

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 ____ 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? ____ 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 file ICTDER03 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.csc.c.unc.edu/ARIC/search.php>

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)?

The following manuscripts are related to the topic but none of them directly addresses the research question proposed here:

- MS #2024: Prehypertension is Associated with Abnormalities of Cardiac Structure and Function in the Atherosclerosis Risk in Communities Study
- MS #1459: Orthostatic change in blood pressure and incidence of atrial fibrillation: results from a bi-ethnic population based study
- MS #1628: Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study
- MS #1578: Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: The CHARGE-AF consortium.

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 at <http://www.csc.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.csc.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 No.

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12. Huxley, Rachel R. 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* 123.14 (2011): 1501–1508. *PMC*. Web. 9 Feb. 2018.
13. Alonso, Alvaro et al. "Incidence of Atrial Fibrillation in Whites and African-Americans: The Atherosclerosis Risk in Communities (ARIC) Study." *American heart journal* 158.1 (2009): 111–117. *PMC*. Web. 7 Feb. 2018.
14. Falcone, Guido and Ji Y. Chong. "Gender Differences in Stroke among Older Adults." *Gender Differences in Stroke among Older Adults*, www.healthplexus.net/article-differences-stroke-among-older-adults. Web. 7 Feb 2018.