ARIC Manuscript Proposal #3412

PC Reviewed: 6/18/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Longitudinal measures of blood pressure and subclinical atrial arrhythmias: The Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Blood pressure and AF and SVE

2. Writing Group:
Writing group members: Faye L. Norby, Alvaro Alonso, Elsayed Z. Soliman, Lin Y. Chen, others welcome

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

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3. Timeline: Statistical analysis: 3 months
Manuscript preparation: 6 months (in conjunction with MESA meta-analysis)

4. Rationale:

Blood pressure (BP) is an important etiologic factor for a variety of cardiovascular outcomes.[1] High BP produces both functional and structural changes in the myocardium, and is associated with an increase in arrhythmias.[2] Understanding how the timing of BP changes and whether prolonged exposure to elevated BP is associated with atrial fibrillation (AF) and supraventricular ectopy (SVE), which includes premature atrial contractions (PACs) and runs of supraventricular tachycardia (SVT), is of importance. AF, a common arrhythmia,[3] is associated with an increased risk of stroke,[4] heart failure,[5] myocardial infarction[6] and death.[7] Recent studies have also found that SVE is associated with increased AF[8] and stroke risk,[9, 10] and thus SVE may be an important biomarker for cardiovascular risk.

Because blood pressure is highly variable throughout the day and from one year to the next, blood pressure assessed on a single occasion results in an incomplete profile of a person's BP.[11] The assessment of serial BP measurements and how changes in BP over time relate to disease risk may inform strategies to more aggressively screen for and treat BP earlier in life.[12, 13] Furthermore, individual BP variability may represent an individual's inability to maintain homeostasis and is an important marker of cardiovascular outcomes.[14] Though long-term BP variability has been studied in relation to atherosclerotic cardiovascular disease (CVD),[15] little is known about associations with AF and other arrhythmias. In ARIC, we have measured associations between BP trajectories and risk of AF and found that those with long-term hypertension had a HR of 1.31 (95%CI 1.14-1.51) for AF compared to those without long-term hypertension.[12]

Clinically-detected AF measured from periodic ECGs, diagnostic codes, and death certificates underestimate the population burden of AF, because AF is often asymptomatic. ARIC and MESA have both conducted long-term ambulatory cardiac monitoring at their respective exam 6 as part of an ancillary study on AF, involving one or two episodes of monitoring (up to 14 days of monitoring from each episode). This extended ECG monitoring provides an unbiased, high-quality assessment of SVE and of AF, whether or not it has been detected clinically previously. We propose using longitudinal measures of BP from all ARIC study visits and measures of AF and SVE from extended ambulatory ECG monitoring to study the relationships between different measures of long-term variation in BP with these atrial arrhythmias.

We plan to conduct similar analyses in the MESA study, and we will either pool data in a single analysis or meta-analyze results from each study.

5. Main Hypothesis/Study Questions:

In this paper, we will address whether the following aspects of BP (for systolic and diastolic BP, and pulse pressure (systolic-diastolic BP)) are associated with monitor-detected AF or supraventricular ectopy.

1. Current BP
2. Long-term BP (mean)
3. BP trend (slope)
4. BP variability

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).

At ARIC visit 6, all participants were invited wear a 2-week continuous ambulatory ECG recording device called the Zio®Patch (iRhythm Technologies, Inc, San Francisco, CA)

Study population

Inclusion criteria:

- ARIC participants who wore the Zio®Patch > 1 day.

Exclusion criteria:

- Participants were exempt from wearing the Zio®Patch if they had skin allergic reactions to adhesive tape, history of pacemaker or defibrillator implantation.
- For the longitudinal analyses, we will require each person to have at least 3 BP measurements (in visits 1-6)

Exposures

Systolic BP (SBP), diastolic BP (DBP), and pulse pressure (PP=SBP-DBP) at ARIC visits 1 – 6

Covariates

Because we plan to define the exposure variable using BP measurements from visits 1-6, we will assess potential confounding variables at visit 1: age, sex, race/study center, weight, height,

glucose status (normal, IFG, untreated diabetes, treated diabetes), use of antihypertensive medications,[a] use of statins, smoking and alcohol use.

[a]These variables will be considered as possible effect

Outcomes

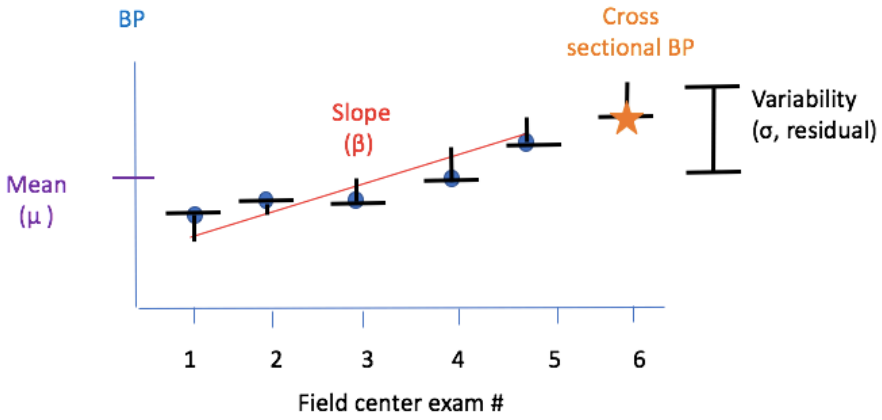
a) AF measures including
    a. Presence of AF on extended ECG monitoring at visit 6, defined as a continuous run of AF or atrial flutter lasting at least 30 seconds.
    b. Burden of AF from extended ECG monitoring at visit 6, defined as the proportion of monitored time that a person is in AF. This outcome will be evaluated only among those with any AF detected on the ECG monitor.
b) SVE measures including:
    a. Frequency of PACs detected on extended ECG monitoring at visit 6 (defined as number of PACSs per hour)
    b. Presence of SVT, defined as 4 or more consecutive PACs
    c. Frequency of runs of SVT per day

Because some participants have zero PACS/hour or runs of SVT/day, we will add a small value (equivalent to the 1st percentile of the distribution in the analysis population) for these variables to every participant.

Analysis Plan:

For each participant, we will use repeated measurements from visits 1-5 and linear regression to estimate within-person mean, trend, and variability in SBP, DBP and PP.[16] We will require each person to have at least 3 BP measurements for analyses of current BP, average BP and BP trend; in the analysis of BP variability, each person will be required to have at least 4 BP values. From the linear regression analysis (Figure), the trend is the BP slope, and the variability is the square root of the variance from the residuals from each individual's regression.

Figure: Various components of BP and how these will be measured



1. Is current BP associated with monitor-detected atrial arrhythmias?

To address whether current BP is associated with AF or SVE, we will conduct cross-sectional analyses with the visit 6 BP. For the binary outcomes (presence of AF, SVT) we will use logistic regression where current BP is the exposure. For the continuous outcomes (burden of AF, PAC frequency, SVT frequency) we will use linear regression where current BP is the exposure. Based on prior work showing that elevated SBP is associated with increased risks of clinically-detected AF, [17] as well as work showing that decreases in DBP in older age are associated with increased risks of disease,[18] we expect that cross-sectional BP will be associated with the presence of monitor-detected AF or SVE.

2. Is mean long-term BP associated with monitor-detected atrial arrhythmias over and above the current BP?

We will estimate the mean BP from Visits 1-5. Average BP will be the exposure in a logistic regression model (presence AF, SVT) or in a linear regression model (burden of AF, PAC frequency, SVT frequency). We will adjust for current (Exam 6) BP. We expect to find that persistently elevated long-term BP (higher mean during Visits 1-5) will be associated with an increased risk of monitor-detected AF or SVE over and above the current BP, because persistently elevated SBP and DBP have been associated with increased rates CVD outcomes.[16, 19]

3. **Is BP trend (slope) associated with monitor-detected atrial arrhythmias over and above the current BP and long-term mean BP (i.e. is it how you get there that matters or just where you are now)?**

To address whether BP trend is related to AF or SVE, independent of current BP and long-term mean BP, we will calculate the slope coefficient in the person-specific linear regression of BP from Visits 1-5. Then, using a logistic model (presence AF, SVT) or a linear regression model (burden of AF, PACS, frequency of SVT) we will ask the following questions:

i) Is BP slope associated with outcomes after adjusting for current BP and long-term mean BP?

ii) In a 2-df test, are BP slope and long-term mean BP associated with outcomes after adjusting for current BP?

4. **Is BP variability an important risk factor for monitor detected AF or SVE above and beyond and average BP and BP trend?**

To address whether greater within-person BP variability increases the risk of AF or SVE, we will determine intra-individual variability calculated as the residuals from each individual's regression. Then in a logistic regression model (presence AF, SVT) or in a linear regression model (burden of AF, PAC frequency, SVT frequency), variability will be the exposure and we will adjust for long-term mean BP and BP trend. We hypothesize that greater BP variability will be associated with increased risks of subclinical AF and SVE compared to those with relatively lower BP variability.

Models:

1. Current BP→Arrhythmias
    a. Logistic AF bp_current + confounders
    b. Logistic SVT bp_current + confounders
    c. Linear AF_burden bp_current + confounders
    d. Linear PACS bp_current + confounders
    e. Linear SVT_frequency bp_current + confounders
2. Long term BP (mean) →Arrhythmias
    a. Logistic AF bp_average bp_current + confounders
    b. Logistic SVT bp_average bp_current + confounders
    c. Linear AF_burden bp_average bp_current + confounders
    d. Linear PACS bp_average bp_current + confounders
    e. Linear SVT_frequency bp_average bp_current + confounders

3. BP trend (slope) → Arrhythmias
    a. Logistic AF bin bp_trend bp_average bp_current + confounders
    b. Logistic SVT bin bp_trend bp_average bp_current + confounders
    c. Linear AF_burden bp_trend bp_average bp_current + confounders
    d. Linear PACS bp_trend bp_average bp_current + confounders
    e. Linear SVT_frequency bp_trend bp_average bp_current + confounders

    These models will be compared to the following referent models:

    i) models with just bp_average, bp_current + confounders (to determine if bp_slope is meaningful)

    ii) a model with just bp_current + confounders (to determine if combined bp_slope and bp_average is meaningful)
4. BP variability → Arrhythmias
    a. Logistic AF bp_variability bp_average bp_trend + confounders
    b. Logistic SVT bp_variability bp_average bp_trend + confounders
    c. Linear AF_burden bp_variability bp_average bp_trend + confounders
    d. Linear PACS bp_variability bp_average bp_trend + confounders
    e. Linear SVT_frequency bp_variability bp_average bp_trend + confounders

Sensitivity analyses

a) MESA participants were free of clinical CVD at baseline, so in order to have comparable study populations for the meta-analysis, we will exclude those in ARIC with CVD at baseline.
b) Many participants have developed intercurrent CVD events (CHD, stroke, HF) during follow-up between Visits 1 and 6, and these CVD events may be potential mediators of potential relationships between longitudinal BP measures and the risk of atrial arrhythmias at Visit 6. For any of the above associations that meet criteria for statistical significance, we will conduct mediation analyses that adjust for intercurrent CVD.
c) Repeating the analyses in a population of participants who do not take anti-arrhythmic medications.
d) Repeating the analyses in a population restricted to those who do not initiate antihypertensive medications during follow-up.
e) Adjusting analyses for left atrium volume or size.

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.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)?
The most relevant manuscripts include:
#2146: SBP trajectories and CVD – Kucharska-Newton
#2018: Blood pressure control and AF – Sellers
#2280: Zio arrhythmia burden - Rooney

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 (2014.18,)
___ 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.

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