ARIC Manuscript Proposal #3425

PC Reviewed: 7/9/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1. a. Full Title:
Association of cardiac biomarkers with supraventricular and ventricular ectopy: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title:
Risk factors for atrial and ventricular ectopy

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

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3. Timeline:
July-August-September 2019 – Complete primary data analysis
October-November-December 2019 – Additional data analysis/Manuscript preparation
October 2019-Submit abstract AHA Epidemiology/Lifestyle
January-February 2020 – Submit manuscript for P&P review

4. Rationale:

Ectopic beats are commonly encountered during outpatient electrocardiographic evaluation. While they are oftentimes asymptomatic and seemingly benign in nature, they are associated with adverse long-term outcomes. Premature atrial contractions (PACs) and subclinical atrial tachyarrhythmias are independent predictors of atrial fibrillation, stroke, and death.[1-6] Similarly, several studies have established that individuals with premature ventricular contractions (PVCs) have a higher risk of ischemic heart disease, stroke, heart failure, and death.[7-13] The increased risk associated with PVCs has been demonstrated in individuals with and without prevalent cardiovascular disease.[10-12, 14, 15] Observed associations appear to be, at least in part, causal as ablation of PVCs reversed functional and structural cardiac changes while ablation of PACs has been associated with higher probability of recurrence-free survival among patients with persistent AF.[16-19]

Due to adverse risks associated with atrial and ventricular ectopy, an enhanced understanding of their causes and risk factors is of major clinical importance. Many population-based studies have reported the frequency of and clinical risk factors for either atrial or ventricular ectopy electric activity in the general population.[20-25] However, a paucity of data is available concerning the association between cardiovascular biomarkers and frequency of arrhythmias in community-based cohorts and these studies have been limited to either N-terminal pro b-type natriuretic peptide or high-sensitivity cardiac troponin.[25, 26] Elevated levels of cardiovascular biomarkers in community-based cohorts are strongly predictive of cardiovascular disease and mortality.[27-29] As these established CV biomarkers are associated with adverse cardiovascular outcomes in the general population, these biomarkers may also predict arrhythmias in the general population

In addition, these studies were limited in that ectopy was assessed either with 2-minute ECG recordings or 24-hour Holter recordings. These methods may not allow adequate time to fully capture the arrhythmia frequency burden. These studies also did not specifically look at whether associations are different with respect to the presence of supraventricular or non-sustained ventricular tachycardia. The Zio patch is a non-invasive, leadless device that provides continuous recording of ECG data over a two-week period and represents an exceptional opportunity to more completely quantify chronic ectopic atrial and ventricular burdens. These data have recently been collected on participants in the Atherosclerosis Risk in Communities (ARIC) study, a well-characterized, biracial cohort. We will assess associations for a panel of different biomarkers of subclinical cardiovascular injury with the presence of both atrial and ventricular ectopy.

5. Study Objective:

- To determine the association of CV biomarkers with burden of
    - Supraventricular ectopy—defined as PAC burden (number of PACs per hour) and SVT frequency (number of SVT episodes per day)
    - Ventricular ectopy—defined as PVC burden (number of PVCs per hour) and NSVT frequency (number of NSVT episodes per day)
- To determine the association of change in CV biomarkers with burden of
    - Supraventricular ectopy
    - Ventricular ectopy

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).

Data:

Study participants

Members of the ARIC cohort attending Visit 6 (2016-2017) with Zio patch ambulatory ECG monitoring (n=2616).

Exposure variables—Biomarkers of subclinical cardiac injury (measured at V6)

1) N-terminal pro b-type natriuretic peptide—NT-proBNP (pg/mL)
2) High-sensitivity Cardiac Troponin T—hs-cTnT (ng/l)
3) Growth differentiation factor-15—GDF-15 (pg/mL)

**Visit 4 hs-cTnT and visit 5 NT-proBNP will also be used as exposure variables to determine the past trajectories of change in biomarkers among people who survived to visit 6. GDF-15 was not measured at prior visits.

Outcome variable— Zio Patch

Participants attending Visit 6 were invited to wear an ambulatory ECG monitor for a period of 2 weeks. The following information will be used from the Zio patch report:

- Supraventricular Tachycardia (SVT), narrow complex tachycardia >4 beats
- SVT frequency, number of SVT episodes per hour
- Premature atrial contraction (PAC) burden, number of PACs per hour
- Premature ventricular contraction (PVC) burden, number of PVCs per hour
- Non-sustained ventricular tachycardia (NSVT), wide complex tachycardia >4 beats
- NSVT frequency, number of NSVT episodes per hour

Covariates

Demographic – Age (y), Race, Sex, Education (<12 yrs), Clinic site

Physical examination – SBP (mmHg), DBP (mmHg), pulse (beats/min), Height (cm), Weight (kg), BMI (kg/m^2), Waist-to-hip ratio (WHR)

Comorbidities – Cigarette smoking (current/former/never & pk-yr), Diabetes (yes/no), Hypertension (yes/no), Stroke (yes/no), ECG-based left ventricular hypertrophy (yes/no), Atrial fibrillation/flutter (yes/no)

Laboratory data – Fasting glucose (mg/dL), eGFR by CKD-EPI cystatin (mL/min/1.73m^2), HgbA1c (%), Total cholesterol (md/dL), High-density lipoprotein cholesterol (mg/dL), hs-CRP (mg/L)

Medication use (yes/no) – Beta-blocker use, Calcium-channel blocker use, Statin use, Anti-hypertensive use, Anti-arrhythmic drug therapy, and Anti-DM use

Others – Alcohol consumption (current/former/never & gm/wk), Physical activity levels (Baecke questionnaire for sport)

**Diabetes will be defined based off Fasting glucose, HgBA1c, and Anti-DM use.

**Hypertension will be based off SBP, DBP, and Anti-hypertensive use

Exclusion criteria

Individuals with prevalent CHD or HF will be excluded. Individuals without V6 exposure, covariate, exposure, or Zio Patch data will also be excluded. Finally, those with underlying atrial fibrillation or atrial flutter will be excluded from the atrial ectopy analysis.

Analysis plan:

Eligible participants not meeting any of the exclusion criteria above will be part of the study analysis (n=2519).

1) Comparison of baseline characteristics

Descriptive statistics will be computed for baseline characteristics. We will examine the distributions of exposure variables stratified according (1) median number of PACs per hour and (2) median number of PVCs per hour.

2) CV biomarker associations with atrial and ventricular ectopy

Linear regression will be used to estimate the associations of CV biomarkers with (1) PAC burden, (2) SVT frequency, (3) PVC burden, (4) NSVT frequency. Outcome variables may need to be log base 2 transformed to meet normality assumptions. Biomarkers will be expressed in units of standard deviation. Estimates for the percentage difference will be presented for each SD increment. Each CV biomarker will be assessed individually after adjustment for covariates listed above. Those biomarkers found to be independently associated with the outcome will be assessed simultaneously in a combined model.

3) Past trajectories of change in biomarkers among people who survived to visit 6 and associations with atrial and ventricular ectopy

The following analysis will be performed for those with hs-cTnT (visit 4) and/or NT-ProBNP (visit 5) measured . GDF-15 was not measured at prior visits.

Linear regression will be used to estimate the associations of change in CV biomarkers with (1) PAC burden, (2) SVT frequency, (3) PVC burden, (4) NSVT frequency. Outcome variables may need to be log base 2 transformed to meet normality assumptions. Change in CV biomarkers will be expressed in units of standard deviation. Estimates for the percentage difference will be presented for each SD increment. If both biomarkers are found to be independently associated with the outcome, then they will be assessed simultaneously in a combined model.

4) Stratified analysis

Analysis in steps #2 and #3 will be repeated stratified by (1) race and (2) gender

7. a. Will the data be used for non-CVD analysis in this manuscript?

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?

8. Will the DNA data be used in this manuscript?

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.

YES

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 author identifies no significantly related manuscript proposals. Co-authors with extensive ARIC experience for prior proposals related to atrial fibrillation and peripheral arterial disease have been contacted to collaborate.

11. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

YES—2013.14 "Significance of Arrhythmias by Novel ECG Monitoring in Community-Dwelling Elderly" (PI: Lin Y Chen)

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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