ARIC Manuscript Proposal # 3174

PC Reviewed: 6/12/18  Status: _____  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1. Full Title:
Quantification of arrhythmia burden in individuals with prevalent peripheral artery disease: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title:
Arrhythmia burden in PAD

2. Writing Group:

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:
June-July-August 2018 – Complete primary data analysis
August-September-October 2018 – Additional data analysis/Manuscript preparation
October 2018-Submit abstract AHA Epidemiology/Lifestyle
November-December 2018 – Submit manuscript for P&P review

4. Rationale:
Over 20% of older men and women seen in primary care medical practices have a low ankle–brachial index (ABI), defined as a value ≤0.9, consistent with peripheral artery disease (PAD). These individuals have higher rates cardiovascular disease and mortality compared to those with a normal ABI. Similarly, those with a borderline ABI (0.91-0.99) also are at increased risk for these outcomes compared to those with a normal ABI. Symptomatic PAD requiring hospitalization is associated with a five-year mortality rate that approaches 25%. Although risk factor management, aspirin, and high-intensity statin are effective in helping reducing this risk, cardiovascular disease and mortality incidence in individuals with PAD remain high.

Cardiac arrhythmias, ranging from increased atrial or ventricular ectopy to clinically manifest atrial fibrillation (AF) or ventricular tachycardia, are associated with increased mortality and may contribute to explain the excess risk observed in PAD. The majority of these, however, are often asymptomatic and clinically unrecognized. AF prevalence and incidence, for example, has been reported to be higher in individuals with PAD compared to those without PAD, but diagnosis of AF in these studies relied primarily on hospitalization or medical claims data. To our knowledge, comprehensive information on the arrhythmic burden in individuals with PAD that includes an asymptomatic assessment has not been published. Assessments of the presence or burden of cardiac arrhythmias in large population-based studies that include individuals with PAD have been limited to standard 12-lead ECGs, 2-minute ECG recordings, and, in a few cases, 24-48 hour Holter recordings. These methods may not allow adequate time for either certain arrhythmias to manifest or full capture of the frequency burden for those that do appear.

The Ziopatch is a non-invasive, leadless device that provides continuous recording of ECG data over a two-week period, and represents an exceptional opportunity to quantify the burden of several types of arrhythmias that have been otherwise difficult to identify. These data have recently been collected on participants in the Atherosclerosis Risk in Communities (ARIC) study, a well-characterized, biracial cohort. We will determine the prevalence of and quantify the burden for clinically significant cardiac arrhythmias, as determined by Ziopatch monitoring, in individuals with PAD compared to those without PAD. Prevalence and incidence of arrhythmias can vary considerably across race. Ventricular arrhythmias, including sudden cardiac arrest and premature ventricular contractions, are higher in African Americans while atrial arrhythmias such as atrial fibrillation are higher in whites. We will also determine whether any differences in associations are observed between African American and white PAD participants.

5. Study Objective:
- To quantify the burden of clinically significant arrhythmias (e.g., atrial ectopy, AF, supraventricular tachycardia (SVT), AV block, ventricular ectopy, and ventricular tachycardia) between those with vs. without PAD
- To investigate whether the burden of arrhythmias in PAD differs by race

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 variable—Peripheral Artery Disease
1) ABI: ABI was measured for participants at visit 6 by trained technicians, using the OMRON VP-1000 plus machine. The ABI was computed by dividing the average of ankle SBP measurements by the average of brachial SBP measurements, usually in the right arm. Two ankle BP measurements were taken 5 to 8 min apart at the posterior tibial artery while the participant was prone in both legs. Consistent with current guidelines, participants will be categorized according to the following values: Low (ABI≤0.9), Borderline (ABI=0.91-0.99), Normal (ABI=1.00-1.40), and Non-compressible (ABI>1.4).16

2) Clinical PAD: To be defined as a prior discharge diagnosis consistent with hospitalized PAD. ARIC cohort members are interviewed twice yearly to ascertain hospital admissions, and the hospital records are reviewed by ARIC staff for all hospital admissions. A trained abstractor obtains and records all ICD-9 hospital discharge diagnoses. Specifically, all records with an International Classification of Disease, Ninth Revision code 440.2 (atherosclerosis of native arteries and extremities), 440.3 (atherosclerosis of bypass graft of the extremities), 440.4 (chronic total occlusion artery extremities), 84.1x (lower-extremity amputation), 38.18 (leg endarterectomy), 39.25 (aorto-iliac-femoral bypass), 39.29 (leg bypass surgery), and 39.50 (PTA of non-coronary vessels) qualified as hospitalized PAD. For hospitalizations occurring after October 2015 we will use the appropriate ICD-10 codes instead. We will contrast participants with clinical PAD at visit 6 vs. those without.

Outcome variable—Zio Patch
Participants attending Visit 6 were invited to wear an ambulatory ECG monitor for a period of 2 weeks. Those who consented wore the Zio patch (iRhythm Technologies, Inc., San Francisco, California). After completing a brief 10-minute questionnaire, the patch was applied to the participants’ left upper chest wall. Participants were instructed to activate the trigger button, integrated into the monitor’s design, should they experience any suspected symptom of arrhythmia and to document the symptoms in a symptom diary. On Day 3 after application, ARIC staff called participants to answer any questions and to encourage participants to wear the device for as long as possible. On Day 10, ARIC staff called to remind them to return the Zio patch and symptom diary to iRhythm Technologies, Inc. The standard Zio Patch report was downloaded from the iRhythm website and verified for accuracy by physician ECG readers at EPICARE (Winston-Salem, North Carolina). The verified and collated data was then sent to the Coordinating Center and integrated into the ARIC database. The following information was collected from the Zio patch report:

- AF, irregularly irregular rhythm with absent P waves lasting >30 seconds (if <30 seconds will be classified as SVT unless AF episodes >30 seconds are evident at other times for the same person)
- AF burden (%), percent of analyzable time in AF
Participants with a 100% burden were considered to have ‘permanent AF’. Those with a percent burden >0 but <100 were considered to have ‘paroxysmal AF’

- 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
- Potentially life-threatening arrhythmias that merited immediate participant notification were also recorded. These included: a) Sustained ventricular tachycardia (VT)—wide complex tachycardia for >30 seconds, b) Ventricular fibrillation (VF), c) Complete heart block, d) Symptomatic 2nd degree atrioventricular (AV) block, Mobitz II, e) pause >6 seconds, f) Symptomatic bradycardia <40 bpm and sustained for >30 seconds.

Other Variables of Interest
Demographic – Age, Race, Sex, Education, Height, Weight, Clinic site
Comorbidities – Cigarette smoking, systolic blood pressure (SBP), diastolic blood pressure (DBP), Coronary heart disease, Heart failure, Stroke, ECG-based left ventricular hypertrophy
Laboratory data – fasting glucose, Hemoglobin A1c (HgbA1c), total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), c-reactive protein (CRP), N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP)
Medication use – Anti-hypertensive use, anti-arrhythmic drug therapy, and anti-DM use
Others – Alcohol consumption, Physical activity levels

Exclusion criteria
Individuals without Zio Patch data, ABI measurement, or necessary covariate data will be excluded. Additionally, individuals were excluded from the low ABI analysis if their ABI was greater than 1.4.

Analysis plan:
Eligible participants not meeting any of the exclusion criteria above will be part of the study analysis.

1) Comparison of baseline characteristics
Descriptive statistics will be computed for all baseline variables. We will examine the distributions of variables across the following ABI categories: Low (ABI≤0.9), Borderline (ABI=0.91-0.99), and Normal (ABI=1.00-1.40). We will also compare baseline characteristics amongst ARIC participants attending Visit 6 who were enrolled in this ancillary study to those who were not enrolled in this ancillary study.

2) Arrhythmic burden across ABI categories
AF prevalence (overall, paroxysmal, and persistent), SVT prevalence and frequency, NSVT prevalence and frequency, PAC frequency, PVC frequency, and potentially life-threatening arrhythmia prevalence will be compared across the 3 ABI categories.

3) Arrhythmic burden according to clinical PAD status
AF prevalence (overall, paroxysmal, and persistent), SVT prevalence and frequency, NSVT prevalence and frequency, PAC frequency, PVC frequency, and potentially life-threatening arrhythmia prevalence will be compared between those with and without clinical PAD.

4) Arrhythmic burden stratified by race in those with a low ABI or clinical PAD

AF prevalence (overall, paroxysmal, and persistent), SVT prevalence and frequency, NSVT prevalence and frequency, PAC frequency, PVC frequency, and potentially life-threatening arrhythmia prevalence will be compared between African-American and white participants with an ABI≤0.9 or a clinical history of PAD.

5) Risk of prevalent arrhythmia or high arrhythmic frequency (defined as top quartile of the overall study population) according to baseline PAD status

- Logistic regression models will be used to calculate adjusted prevalence odds ratios (PORs) and 95% confidence intervals (CIs) for risk of AF (overall, paroxysmal, and persistent), SVT, NSVT and potentially life-threatening arrhythmia according to (1) ABI status (referent=normal ABI) and (2) clinical PAD status (referent=no clinical PAD).
- Similar modeling will be used to calculate adjusted PORs and 95% CIs for risk of high frequency of SVT, NSVT, PACs, and PVCs.
- Model 1 will be adjusted for: age, race, sex, education, and site
- Model 2 will be adjusted for: Model 1 + cigarette smoking, alcohol consumption, DM, SBP, DBP, TC, HDL cholesterol, BMI, physical activity, eGFR, anti-hypertensive use, aspirin use, and statin use, CHD, HF, and stroke

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—“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.

References