1.a. Full Title: Prevalence of atrial fibrillation, its sub-types, and other subclinical arrhythmias among community-dwelling individuals: the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Zio arrhythmia burden (2 weeks)

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

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3. Timeline: All data are available. A manuscript draft will be submitted to the ARIC publication committee within 6 months of approval.
4. **Rationale:**

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with an estimated lifetime risk of 1 in 4.\(^1\) AF is associated with an increased risk of stroke, heart failure, mortality and reduced quality of life.\(^2\) Importantly, among AF patients, anticoagulant use is associated with a 64% reduction in stroke risk and 20% reduction in mortality.\(^3\) AF can be asymptomatic particularly when episodes are intermittent, and it is not uncommon to detect AF for the first time during a post-stroke work-up. However, ECG monitoring has evolved drastically in recent years permitting a longer monitoring period and better characterization of arrhythmia burden.\(^4\)-\(^6\)

The Zio\textsuperscript{®} XT Patch (iRhythm Technologies; San Francisco, CA) is a novel leadless, ambulatory ECG monitoring device and is recommended to be worn for 2 weeks. Little is known about the prevalence of subclinical AF and AF burden over longer-term ECG monitoring in community-dwelling participants. Research involving longer-term ECG monitoring has been reported in patients with a clinical indication (e.g. stroke patients or AF patients). Among those with paroxysmal AF, time to first AF episode and time to first symptomatic AF episode were inversely related to AF burden.\(^7\) A comparison study was conducted in 49 patients undergoing AF management, of which 35% had paroxysmal AF during 2 weeks of Zio\textsuperscript{®} XT Patch monitoring but no AF based on 24 hour Holter monitoring.\(^8\)

Even less is known about the prevalence and burden of arrhythmias other than AF in a community-based setting. In ARIC, for instance, a 2-minute ECG strip was conducted at visit 1; the prevalence of premature ventricular contractions (PVCs) was 6%.\(^9\) Such short-term ECG monitoring may result in an under-estimation of prevalence of arrhythmias and may not permit characterization of arrhythmia burden.\(^1\)

A recent Scientific Statement from the American Heart Association highlighted crucial knowledge gaps surrounding AF burden, including estimating the prevalence of subclinical AF as well as identifying risk factors and determinants for AF burden in a community-based population.\(^10\) In this context, using data from the recently completed ARIC ancillary study (2014.18), we will characterize the prevalence of AF, its subtypes and other subclinical arrhythmias over 2 weeks of continuous ECG monitoring among elderly community-dwelling participants.

5. **Main Hypothesis/Study Questions:**

- To assess the prevalence and burden of AF, its subtypes and other arrhythmias among visit 6 ARIC participants.
- To compare characteristics of those without AF to those with subclinical AF (detected on the Zio\textsuperscript{®} XT patch) or clinical AF (defined by ARIC ascertainment and self-reported AF at visit 6).

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).
This paper will be cross-sectional at visit 6. Participants were asked to wear the Zio® XT Patch for 14 days. ARIC visit 6 participants with ≥48 hours of analyzable Zio® XT Patch ECG data will be eligible for these analyses.

**AF definitions**

Clinical AF = AF based on prior ARIC ascertainment through most recent available or self-report physician diagnosis on visit 6 ZIO questionnaire

Subclinical AF = AF detected on the Zio® XT Patch but no known AF based on ARIC ascertainment or self-report physician diagnosis on visit 6 ZIO questionnaire

**Covariates**

Age, race, sex, study center, body mass index, systolic and diastolic blood pressure, antihypertension medication use, heart failure, diabetes, coronary heart disease, stroke, left atrial volume index

**Statistical analysis**

We will report participant characteristics (described above) stratified by AF status (no AF, subclinical AF, clinical AF) using means±standard deviations and proportions. Chi-squared tests and studentized t-tests will be used to compare characteristics across AF status. Logistic and linear regression will be used to provide compare participant characteristics by AF status with adjustment for age, sex and race. Data are available on presence of AF, percent time spent in AF, and time to first AF episode.

We will report the prevalence of AF, its subtypes, time to detection, and percent time in AF. We will also compare AF detection rate with self-reported AF, AF history from ARIC study (previous hospitalizations or study visit ECGs) as well as oral anticoagulation use at visit 6. In addition to AF prevalence and burden overall, we will provide the results stratified by race and sex.

We will report prevalence and burden (e.g. total number of episodes; duration/total recording time) for the following abnormalities: a) ventricular tachycardia, b) supraventricular tachycardia, c) sinus pauses, d) AV blocks (Type II-b), e) supraventricular ectopy and f) ventricular ectopy.

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.unc.edu/ARIC/search.php

___ x___ Yes (overlap; justification below) ______ No

MP#2280 relates to Ziopatch pilot data collected at visit 5 in n~325. We will utilize similar methods as described in MP#2280 for visit 6 (n~2600). Importantly, we now have Ziopatch data in n~2600 participants at visit 6. All analyses will be based on visit 6 data.

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)?

MP2280 (Agarwal) AF and subclinical
MP3117 (Rooney) Zio repeat diagnostic yield

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 (list number* 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.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.
References