

## ARIC Manuscript Proposal # 3117

PC Reviewed: 2/13/18  
SC Reviewed: \_\_\_\_\_

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Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Incremental diagnostic yield of extended ambulatory electrocardiogram monitoring for the detection of subclinical arrhythmias: the Atherosclerosis Risk in Communities (ARIC) study

**b. Abbreviated Title (Length 26 characters):** Zio repeat diagnostic yield

### 2. Writing Group:

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

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### 3. Timeline:

Mid-2018: Once visit 6 data are finalized, we will proceed with analyses and manuscript preparations.

#### 4. Rationale:

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with an estimated lifetime risk of approximately 1 in 4.<sup>1</sup> AF can be asymptomatic and may often go undetected, particularly when episodes are intermittent. This is termed subclinical AF and can result in an underestimation of the population burden of AF.<sup>1</sup> Long-term, continuous ambulatory electrocardiographic (ECG) monitoring has evolved in recent years. There is growing interest in ambulatory ECG patch monitoring which allows extended wear time beyond the traditional 24-48 hours of Holter monitoring to improve AF detection in research and clinical settings.<sup>2-4</sup>

The Zio<sup>®</sup>XT Patch (iRhythm Technologies; San Francisco, CA) is a novel leadless, ambulatory ECG monitoring device which is recommended to be worn for 2 weeks. Little is known about the diagnostic yield of extending ECG monitoring beyond 2 weeks on subclinical AF detection, particularly among individuals without a clinical indication. Even less is known about the diagnostic yield in relation to prevalence and burden of other arrhythmias such as non-sustained ventricular tachycardia (NSVT) and premature atrial contractions (PACs).

The majority of studies that have examined the incremental diagnostic yield have compared 14 day wear time (Zio<sup>®</sup>XT Patch) to 24-48 hours (as would be identified on a Holter monitor).<sup>5-10</sup> All these studies are also comprised of individuals with a clinical indication for ECG monitoring (e.g. high risk for AF, managing AF, discharged from ED, stroke patients). Rosenberg et al (2013) compared the Holter monitor (24 hours) and Zio<sup>®</sup>XT Patch (2 weeks) undergoing AF management. They found that 17 of 49 patients (35%) with no AF based on the Holter had paroxysmal AF based on 2 weeks monitoring.<sup>8</sup> Turakhia et al (2013) compared diagnostic yield of the 14 days wear time to the first 48 hours among those with paroxysmal AF. They also found that time to first AF episode and time to first symptomatic AF episode were inversely related to AF burden.<sup>10</sup>

Several studies have examined the diagnostic yield beyond 2 weeks monitoring; however, this screening has been limited to those with prior stroke or transient ischemic attacks. In a meta-analysis of RCTs among those with cryptogenic stroke, AF was identified in 15% of patients with 30 day ECG monitoring but only 4% of patients with 24 hours of monitoring.<sup>11</sup> Recently, the ASSERT-II trial assessed 256 patients at neurology or cardiology clinics without a history of AF. Based on an average of 16 months of sub-cutaneous ECG monitors, the median weekly burden of subclinical AF was 3 minutes and mean time to first AF episode was 5 months. In subgroup analyses, subclinical AF was more common in those with left atrial enlargement but subclinical AF did not differ by prior stroke.<sup>12</sup>

Although prior studies suggest that longer ECG monitoring detects more arrhythmias, it is unknown how or whether prolonged ECG monitoring improves detection in community-dwelling individuals. The ARIC cohort is uniquely suited to answer this question because a subset of visit 6 participants were invited to wear the Zio<sup>®</sup>XT Patch twice, each time for up to 14 days. We aim to examine whether prolonging the Zio<sup>®</sup>XT Patch wear time – for a total duration of up to 28 days – improves the diagnostic yield of subclinical arrhythmias.

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

Aim 1: To compare the wear time and analyzable time of the second 2 weeks of the Zio<sup>®</sup>XT Patch monitoring to the first 2 weeks.

Hypothesis: We hypothesize that the wear time and analyzable time of the second 2 weeks of Zio<sup>®</sup>XT Patch monitoring will be the same as the first 2 weeks.

Aim 2: To determine the diagnostic yield of wearing the Zio<sup>®</sup>XT Patch device for 4 weeks as compared to 2 weeks on the prevalence and burden (% analyzable time spent in AF) of subclinical AF.

Hypothesis: Prolonged ECG monitoring for 4 weeks will modestly increase detection of subclinical AF beyond 2 weeks.

Aim 3: To determine the diagnostic yield of wearing the Zio<sup>®</sup>XT Patch device for 4 weeks as compared to 2 weeks on the prevalence and burden of other arrhythmias such as SVT, NSVT, PACs, PVCs.

Hypothesis: Prolonged ECG monitoring for 4 weeks will modestly increase detection of other arrhythmias beyond 2 weeks.

## **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**

Cross-sectional at visit 6 at the Minnesota, Washington County and Jackson sites

### **Study population**

Inclusion criteria:

- Between July 2016 to January 2018, N~ 400 ARIC study participants who attended visit 6 wore the Zio<sup>®</sup>XT Patch device twice, each time for up 2 weeks.

Exclusion criteria:

- Those who wore the Zio<sup>®</sup>XT Patch for less than 2 days
- Participants with a history of AF as defined by ARIC ascertainment and based on self-report of a physician diagnosis of AF at ARIC visit 6.

### **Exposures/Outcomes**

Participants were asked to wear a Zio<sup>®</sup>XT Patch for 14 days twice. The first device was applied at the ARIC study visit 6. Participants were asked to self-apply or come into the study clinic for staff to apply the second device approximately 4 days after removing the first device.

Data are available on presence and burden of AF, SVT, NSVT, PACs and PVCs. Participants were also asked to press the button on the Zio<sup>®</sup>XT Patch when they felt symptomatic arrhythmias.

### **Covariates**

Age, sex, race/center, stroke, coronary heart disease, heart failure, diabetes, smoking status, body

mass index, systolic and diastolic blood pressure, antiarrhythmic medication use, antihypertensive medication use, anticoagulant medication use, mild cognitive impairment / dementia

Covariates will be based on visit 6 data.

### **Data analysis**

Aim #1: We will describe characteristics of those who wore the Zio<sup>®</sup>XT Patch for  $\leq 28$  days using the covariates specified above. We will compare the first 2 weeks and the second 2 weeks of the Zio<sup>®</sup>XT Patch. Specifically, we will compare mean wear and analyzable time and the proportion of wear time  $\geq 7$ ,  $\geq 10$  and  $\geq 12$  days. Continuous variables will be compared using a paired t-test and proportions will be compared using a Pearson chi-squared test.

Aim #2: We will report the prevalence of any AF based on  $\leq 14$  days of ECG monitoring and AF prevalence based on  $\leq 28$  days. Crosstabs will be used to compare agreement i.e. AF (or no AF) on the first Zio<sup>®</sup>XT patch vs. second Zio<sup>®</sup>XT patch using the kappa statistic.

Continuous variables will be compared using a paired t-test and proportions will be compared using a Pearson chi-squared test. Participant characteristics will be compared to assess subgroups with a higher prevalence of AF identified through 28 days of ECG monitoring. Cochran-Mantel-Haenszel test statistics will be used to test for interactions among categorical characteristics.

We will estimate the mean duration before the first episode of paroxysmal AF. Cumulative frequency of atrial fibrillation will also be explored using Kaplan-Meier statistics and curves. Depending on the distribution of AF burden, we will examine the time to the first AF stratified by burden (e.g. tertiles, quartiles).

We will consider the following:

- Interactions by age, stroke, mild cognitive impairment / dementia
- We will consider looking at time to first symptomatic AF in a similar approach as specified above

Aim #3: A similar analytic approach as described for Aim #2 will be taken to examine the diagnostic yield of 4 weeks vs 2 weeks ECG monitoring on detection of prevalence and burden of SVT, NSVT, PACs, PVCs.

**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>

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)?

#2280 Prevalence of Atrial fibrillation, its sub-types, and other subclinical arrhythmia among elderly in community using long term ECG recoding (Argawal)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  Yes  No

11.b. If yes, is the proposal

- 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/atic/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/atic/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](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](mailto:pingping_wu@unc.edu). I will be using CMS data in my manuscript  Yes  No.

## References

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4. Mittal S, Movsowitz C, Steinberg JS. Ambulatory External Electrocardiographic Monitoring: Focus on Atrial Fibrillation. *Journal of the American College of Cardiology*. 2011/10/18/ 2011;58(17):1741-1749.
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10. Turakhia MP, Hoang DD, Zimetbaum P, et al. Diagnostic utility of a novel leadless arrhythmia monitoring device. *Am J Cardiol*. Aug 15 2013;112(4):520-524.
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12. Healey JS, Alings M, Ha AC, et al. Subclinical Atrial Fibrillation in Older Patients. *Circulation*. 2017.