1.a. Full Title: Temporal patterns of paroxysmal atrial fibrillation among community-dwelling individuals: the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Temporal patterns of AF

2. Writing Group:

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

First author: Jonathan Kim
   Address: Division of Biostatistics
            School of Public Health
            A460 Mayo Building MMC 303
            420 Delaware St. SE
            Minneapolis, MN 55454

   Phone: (612) 626-9679
   E-mail: kim00225@umn.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
   Name: Lin Y Chen MD MS
   Address: Cardiovascular Division
            Department of Medicine
            University of Minnesota Medical School
            420 Delaware St SE, MMC 508
            Minneapolis, MN, 55455

   Phone: (612) 625-4401
   Fax: (612) 626-4411
   E-mail: chenx484@umn.edu
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 a serious public health problem because of its increasing incidence and prevalence and its association with ischemic stroke, heart failure, dementia, and death.\(^1\) AF can be subclinical and is reported to occur in approximately 30% of individuals who experience an ischemic stroke.\(^2\) Efforts to screen for subclinical AF face many challenges, one of which is its intermittent nature, frustrating attempts to capture it by heart rhythm monitoring.

Circadian rhythmicity has been reported for cardiovascular events including arrhythmias. For example, Clair et al. reported that the frequency of paroxysmal supraventricular tachycardia (SVT) was lowest between midnight and 4 AM and peaked between 4 PM and 8 PM.\(^3\) Similarly, Lee et al. observed nearly equal peaks in the frequency of SVT in the time periods from 8:00 to 9:00 AM, 12:00 to 1:00 PM, and 5:00 to 6:00 PM, with a trough at night.\(^4\) Culic et al. found that SVT can be triggered by periods of increased physical activity and meteorological factors\(^5\). However, little is known regarding the temporal patterns, particularly circadian rhythmicity of AF.

The Zio® XT Patch (iRhythm Technologies; San Francisco, CA) is a novel leadless, ambulatory ECG monitoring device that can be worn for up to 2 weeks. The availability of 2-week heart rhythm data in more than 2,600 participants in ARIC at Visit 6 will allow us to characterize temporal pattern of AF episodes (time during the day, days of the week, and months or seasons of the year). Findings from this inquiry may inform the optimal time to screen for subclinical AF.

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

**Aim:** To examine temporal patterns of paroxysmal AF episodes. Specifically, we aim to characterize variability in AF episodes by time intervals during the day, days of the week, and months or seasons of the year.

**Hypotheses:** There is temporal variability in the frequency and duration of AF episodes. AF episodes are more likely to occur in time periods associated with more activity. As such, AF episodes are highest in the afternoon and lowest after midnight. AF episodes are more frequent on Mondays and Tuesdays and least frequent on weekends. AF episodes are more frequent in summer months and less in winter months.

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 analysis 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**
Defined as irregularly irregular rhythm >30 secs in the absence of P waves
We will examine both frequency and duration of AF episodes. We will only be considering those with paroxysmal AF so those with continuous AF will be excluded.

**Covariates**
Age, race, sex, study center, heart failure, hypertension, diabetes, coronary heart disease.

**Statistical analysis**
We will perform Poisson regression using Generalized Estimating Equations to estimate the effect of different temporal periods (e.g. time of day, day of week, season of year) on the expected count of AF episodes. We will divide each individual’s two-week monitoring data into 3-hour intervals and count the number of AF episodes within each interval. These counts will be used as the outcomes for a log-linear Poisson GEE regression model with time of day, day of week, and season as covariates. The GEE approach is used to account for the correlation of 3-hour intervals from the same individual. We will adjust for demographic and health-related covariates (see list above). In a similar manner, we will also examine temporal patterns in relation to length of episodes using linear regression GEE and time spent in AF as the response variable. Data are available on presence of AF, percent time spent in AF, number of AF episodes, and time of first AF episode.

We will report identified temporal patterns of AF burden. In addition to temporal patterns in AF prevalence, we will examine the results stratified by clusters of patients with similar demographic characteristics. We will report any identified patterns among such subgroups.

7.a. Will the data be used for non-CVD analysis in this manuscript? ___ Yes   ___ 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   ___ 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/mantrack/maintain/search/dtSearch.html

______ Yes (overlap; justification below)  ___x____ 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)?

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 Chen)

___ ____ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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