ARIC Manuscript Proposal #3406

PC Reviewed: 6/18/19    Status: _____    Priority: 2
SC Reviewed: _________    Status: _____    Priority: _____

1.a. Full Title: Diurnal patterns of arrhythmias by chronic kidney disease (CKD) status using continuous heart rhythm monitoring for two weeks

b. Abbreviated Title (Length 26 characters): Diurnal patterns of arrhythmias by CKD

2. Writing Group: Esther Kim, Vadim Zipunnikov, Elsayed Soliman, Josef Coresh, Kunihiro Matsushita, Lin Yee Chen

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

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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).

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3. Timeline: Once the proposal is approved, we will begin analysis using available data from the ARIC study visit 6. A manuscript will be finalized a few months after approval.
4. Rationale:

Chronic kidney disease (CKD) has been associated with arrhythmias, especially atrial fibrillation and arrhythmia-related outcomes such as sudden cardiac death in several previous studies.\(^1\) However, most of these studies have looked at the presence or occurrence of these arrhythmias as dichotomous outcomes, and thus diurnal patterns of arrhythmias are yet to be characterized.

To date, a few studies have explored circadian rhythms of arrhythmias. However, these studies have examined mostly atrial fibrillation or malignant ventricular arrhythmias resulting in an implantable cardioverter defibrillator (ICD) shock or sudden cardiac death.\(^2-10\) For studies that examined atrial fibrillation, the episodes were detected using either a 24-hour Holter monitor or a transtelephonic 3-lead or 12-lead ECG, which allowed individuals to briefly record and transmit ECGs during onset of symptoms.\(^9,10\) Taken together, these studies were limited by focusing on only the most lethal episodes (resulting in ICD shock or death), relatively short monitoring period (using 24-hour Holter monitoring) or including only symptomatic cases (using transtelephonic ECGs). Furthermore, past studies have mostly focused on highly selected group of patients (i.e., those who have structural cardiac disease or have ICDs) and were unable to investigate how different clinical (e.g., CKD, diabetes, etc.) and demographic (e.g., age, sex, race, etc.) characteristics can influence the diurnal patterns.

Using data from the ARIC study, we can overcome these caveats, as there are two-week continuous ECG data for many types of arrhythmia collected in a large community-based cohort. Furthermore, we can leverage newer statistical methods for functional data analysis to better characterize diurnal patterns.\(^11\) We therefore propose to characterize the diurnal patterns of a few major arrhythmias (e.g., atrial fibrillation, non-sustained ventricular tachycardia, long pause, and atrioventricular block) and how they vary by CKD status using the Zio Patch, an FDA-approved device for 2-week ECG monitoring. Findings from this study can provide insights into unique underlying mechanisms of different arrhythmias and identify high-risk time windows that can inform the optimal timing of ECG monitoring or potential treatment.

5. Main Hypothesis/Study Questions:

To characterize the diurnal patterns of a few major arrhythmias (atrial fibrillation, non-sustained ventricular tachycardia, long pause, atrioventricular block) and how the patterns vary by CKD status.

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).

We will include all black and white ARIC study subjects with kidney disease measures (serum creatinine and cystatin C and albuminuria) and complete Zio Patch evaluation. Participants with missing kidney disease measures or Zio Patch data will be excluded. We will use data from visit 6.

Main exposures:
• CKD status as a binary variable (no CKD vs CKD) or as a categorical variable (no CKD, CKD with moderate risk, CKD with high risk, CKD with very high risk), defined using eGFR and albuminuria according to the KDIGO guidelines
• eGFR will be calculated using age, sex, race, serum creatinine and cystatin C using the CKD-EPI equation
• Albuminuria will be measured using urinary albumin-to-creatinine ratio (ACR)

Outcomes:
• Diurnal patterns of:
  - Atrial fibrillation/flutter
  - Non-sustained ventricular tachycardia
  - Long pause (>3 seconds)
  - 2nd (type II) and 3rd degree atrioventricular block

  using episodic data from the Zio Patch.

Covariates:
• Sociodemographic factors (age, sex, race, education)
• Physical information (body mass index, blood pressure)
• Lifestyle factors (smoking status, alcohol habit, physical activity)
• Comorbidities (hypertension, coronary heart disease, diabetes, dyslipidemia, stroke)
• Inflammation (C-reactive protein)
• Cardiac parameters (left ventricular mass index, left ventricular ejection fraction)
• Medications (QT-prolonging, antiarrhythmic, antihypertensive medications)

Statistical analysis:
For each arrhythmia type:
1) Compare baseline characteristics by CKD status and by the presence of arrhythmia using descriptive statistics (mean [SD], median [IQI], frequency [%]) and tests (t-test, ANOVA, chi-square).

2) For every individual with intermittent arrhythmia, plot episode onset and duration by day and over 24 hours to visually inspect any patterns or potential outliers.

3) Format the episodic dataset so that the presence of arrhythmia is recorded in moving time-windows for each day. For example, for a 10 minute time window with 5 minutes of overlap between the windows, there will be 288 time windows for each day. We will explore different time window lengths.

4) To visualize a crude diurnal pattern, create a probability plot of an arrhythmia by plotting the presence of arrhythmias (summarized over the 14 days) over 24 hours, and fitting binomial smoothing curves.
5) To characterize the diurnal pattern for the arrhythmia and to study how the patterns differ by CKD and other covariates, fit a generalized multilevel function-on-scalar regression, which involves two steps:
- For each time point, fit a generalized linear model accounting for CKD and other covariates, accounting for subject-specific and subject/day-specific deviation from the mean
- Smooth the beta coefficients as a function of time
- Create a confidence interval by bootstrapping

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.cscc.unc.edu/ARIC/search.php

_X__ 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)?
There are a few existing proposals for CKD and some arrhythmias such as atrial fibrillation (#1627) and sudden cardiac death (#1244 and #2202), but none of them include Zio Patch data.

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.cscc.unc.edu/aric/forms/](http://www.cscc.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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.unc.edu/aric/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. I will be using CMS data in my manuscript ____ Yes __X__ No.

References