ARIC Manuscript Proposal # 3073

PC Reviewed: 11/14/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Presence, frequency, and duration of cardiac arrhythmias over two weeks in chronic kidney disease: the ARIC study

b. Abbreviated Title (Length 26 characters): 2-week arrhythmias in CKD

2. Writing Group:
Writing group members: Esther Kim, 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]**

First author: Esther Kim
Address: Welch Center for Prevention, Epidemiology, and Clinical Research
2024 E. Monument St., B-331, Baltimore, MD 21287
Phone: (443) 559-1504
E-mail: ekim143@jhu.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: Kunihiro Matsushita
Address: Welch Center for Prevention, Epidemiology, and Clinical Research
2024 E. Monument St., Suite 2-600 (Rm 2-602), Baltimore, MD 21287
Phone: (443) 287-8766 Fax: (410) 367-2384
E-mail: kmatsus5@jhmi.edu

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 complete visit 6 data become available.

4. Rationale:

Chronic kidney disease (CKD) characterizes a reduced kidney function or kidney damage, and affects more than 10%-15% of the adult population globally[1]. Compared to the general population, CKD patients have an alarmingly higher rate of mortality, with sudden cardiac death (SCD) accounting for up to 25% of all deaths in this clinical population[2]. The underlying pathogenesis of arrhythmia in CKD is unclear and complex, but most likely involves an abnormal myocardium that is vulnerable to irregular ventricular conduction and various arrhythmogenic triggers such as electrolyte abnormality or uremic toxins [2].

Typically, an electrocardiogram (ECG) is used to non-invasively detect abnormal electronic conduction or arrhythmias and identify patients at risk; however, the conventional practice of using a 10-second ECG or a 24-hour Holter monitor often misses arrhythmias, as many are transient or paroxysmal. In this context, a novel leadless ECG-patch (Zio Patch, iRhythm Technologies, USA) has been introduced as a new device for continuously monitoring heart rhythm for up to 14 days[3]. Zio Patch has been shown to detect more events than a Holter monitor and is cleared by Food and Drug Administration for clinical use[3]. However, no studies have investigated the value of this novel device to monitor the high-risk CKD population. Moreover, no information is available regarding any specific risk factors of arrhythmias in persons with CKD. We therefore propose to analyze Zio Patch and clinical data from ~4,000 participants in the Atherosclerosis Risk in Communities (ARIC) study.

5. Main Hypothesis/Study Questions:

Aim 1) Examine the burden (i.e., presence, frequency, and duration) of various arrhythmias by CKD status (i.e., different stages of CKD and no CKD) defined by estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio. We hypothesize that more severe CKD will be associated with higher burden of arrhythmias.

Aim 2) Identify potent predictors of various arrhythmias in participants with CKD. We are particularly interested in electrolyte imbalance (i.e., serum potassium, calcium, magnesium) and anemia as key CKD complications increasing the risk of arrhythmias in CKD. We will evaluate predictors of arrhythmias are (dis)similar among those with vs. without CKD. Since there are no established treatments to recover reduced kidney function at this moment, this aim will have implications for the management of arrhythmia risk in CKD.

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).

For both aims, 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 the ARIC study visit 6 data for Aim 1 and additionally include visit 5 data for Aim 2.

Main exposures:

Aim 1)

- eGFR (calculated using age, sex, race, serum creatinine and cystatin C using the CKD-EPI equation)
- Urinary albumin-to-creatinine ratio (ACR)

Aim 2)

- Serum electrolytes (serum potassium, calcium, magnesium)
- Anemia (hemoglobin)

Outcomes:

- Arrhythmia and heart rate/conduction parameters of interest
    - Composite event comprised of:
        - Atrial fibrillation/flutter
        - 2nd (type II) and 3rd degree atrioventricular block
        - Pause > 3 seconds
        - Ventricular tachycardia
        - Ventricular fibrillation
    - A secondary composite event comprised of:
        - Atrial fibrillation/flutter
        - 2nd (type II) and 3rd degree atrioventricular block
        - Pause > 3 seconds
        - Ventricular tachycardia
        - Ventricular fibrillation
        - Supraventricular tachycardia
    - Separately examine:
        - Atrial fibrillation/flutter
        - 2nd (type II) and 3rd degree atrioventricular block
        - Pause > 3 seconds
        - Ventricular tachycardia
        - Ventricular fibrillation
        - Supraventricular tachycardia
        - Supraventricular and ventricular ectopy
- Additional characteristics of arrhythmia:
    - Burden characterized by % of analyzable time
    - First occurrence – elapsed time in days
    - Longest duration
    - Longest episode beat count
    - Maximum heart rate

Covariates (will be explored as predictors in Aim 2):

- 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:

Aim 1)

- ANOVA or chi-square test will be used to describe and compare baseline characteristics across eGFR and ACR. We will use clinical categories of eGFR and ACR (eGFR: <15, 15-29, 30-44, 45-59, 60-89, and 90+ ml/min/1.73m^2 and ACR: <30, 30-299, and 300+ mg/g).
- Modified Poisson, logistic or linear regression will be used to compare the presence, frequency, and duration of various arrhythmias across eGFR and ACR categories. We will account for potential confounders as listed above.
- We will explore whether the associations are consistent across several demographic and clinical subgroups (by age, gender, race, diabetic status, a history of cardiovascular disease, etc.).

Aim 2)

- For arrhythmias significantly related to CKD in Aim 1, modified Poisson or logistic regression will be used to explore whether serum potassium, calcium, magnesium, and hemoglobin as well as predictors listed in the section of covariates for Aim 1 above are associated with burden of the arrhythmias in CKD beyond kidney function and albuminuria.
- Once we identify significant predictors, we will examine whether those predictors are uniquely strongly associated with those relevant arrhythmias in CKD or have similar patterns in non-CKD. Interaction will be evaluated with a likelihood ratio test for models with vs. without a product term of a predictor of interest and CKD status.

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/

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.

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

1. Hallan SI, Coresh J, Astor BC, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *Journal of the American Society of Nephrology : JASN.* 2006;17(8):2275-2284.
2. Parekh RS, Meoni LA, Jaar BG, et al. Rationale and design for the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease (PACE) study. *BMC Nephrol.* 2015;16:63.
3. Barrett PM, Komatireddy R, Haaser S, et al. Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring. *Am J Med.* 2014;127(1):95 e11-97.

4. Lange T, Rasmussen M, Thygesen LC. Assessing natural direct and indirect effects through multiple pathways. *Am J Epidemiol.* 2014;179(4):513-518.
5. Vart P, Gansevoort RT, Crews DC, Reijneveld SA, Bultmann U. Mediators of the association between low socioeconomic status and chronic kidney disease in the United States. *Am J Epidemiol.* 2015;181(6):385-396.