ARIC Manuscript Proposal #3410

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

1.a. Full Title:
Association of Long-term RR and QT Interval Variability with Cardiovascular Outcomes

b. Abbreviated Title (Length 26 characters):
Long-term QT variability analysis

2. Writing Group:
Writing group members: Hau-Tieng Wu, Jonathan Kim, Julian Wolfson, Faye Norby, Alvaro Alonso, Elsayed Z. Soliman, Lin Y. Chen

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

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3. Timeline: Statistical analysis: 3 months
Manuscript preparation: 2 months

4. Rationale:

With the emergence of long-term electrocardiogram (ECG) recordings that extend several days beyond the typical 24-48 hours, the development of new tools to measure heart rate variability (HRV) and QT interval variability (QTV) are needed to realize the full potential of extra-long-term ECG recordings (14 days or longer). While it has been well known that reduced HRV is associated with increased risk of morbidity and mortality, most studies have been based on short term ECG analysis.

Recently, increased QTV has been reported to be associated with arrhythmia and cardiovascular death (1). While HRV and QTV contain different clinical information, the nonlinear relationship between the RR interval and QT interval is also known to provide useful clinical information. Specifically, the QT correction based on the RR interval (RRI) is known to be useful for drug-prolonged QTc assessment (2,3). While not yet widely explored, it is reasonable to hypothesize that the variability of the relationship between the RRI and QT also provides useful clinical information. However, the non-stationary dynamic nature of the heart rate renders quantification of HRV and QTV a difficult task, not to mention the variability of the relationship between the RRI and QT. Specifically, while there have been several methods proposed to quantify the HRV from 24-48 hour long-term electrocardiogram (ECG) recordings, most of them are based on the stationarity assumption (4-7), a common assumption in many time series techniques. While those methods could still be applied to any non-stationary time series, such as 24-48 hour long-term heart rate, the results might not be directly interpretable, and we might miss the finer non-stationary dynamics. Even worse, it might be misleading, like the typical example discussed in (8). For example, the evidence shown in (8) indicates that as the cardiac vagal tone falls with increasing levels of exercise, a greater percentage of the residual power of the high frequency component may be due to non-neural mechanisms. The problem becomes more challenging when we have “extra-long-term” ECG signals, such as 14 days or longer (9-10).

Recently, we developed a new nonlinear-type time frequency analysis tool to analyze this kind of extra-long-term ECG signals, specifically for the HRV and QTV (11). We would like to assess the association of HRV and QTV (measured from extra-long ECG data available from the Zio XT patch at Visit 6) with prevalent cardiovascular.

5. Main Hypothesis/Study Questions:

Aim 1: Evaluate the association of HRV and QTV with prevalent cardiovascular outcomes
Hypothesis: Lower HRV and higher QTV will be associated with higher prevalence of atrial fibrillation (AF), coronary heart disease (CHD), and heart failure (HF).

Aim 2: Evaluate the coupling between RR interval and QT interval
The less variability in the relationship between the extra-long term RR interval and QT interval, the higher the prevalence of cardiovascular outcomes.

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 Population
Inclusion: ARIC visit 6 participants with ≥48 hours of analyzable Zio® XT Patch ECG data.
Exclusion: Participants with continuous AF during the 2-week recording, which would confound HRV and QTV analysis

Exposures
We consider three sets of exposures determined from the extra-long-term ECG, including the HRV-related indices, the QT variability-related indices, and the indices quantifying the relationship between the RRI and QT interval.

The HRV-related indices include but are not limited to the time-varying high frequency power (tvHF), the time-varying low frequency power (tvLF), the time-varying low-high frequency power ratio (tvLHR) (12), the nonrhythmic-to-rhythmic ratio (NRR) (13). The tvHF, tvLF and tvLHR are generalizations of the traditional high frequency power, low frequency power and low-high frequency power ratio for the sake of capturing the dynamics. The NRR captures how rhythmic the RRI time series is. The traditional HRV indices (i.e., SDNN, RMSSD, etc) are also included for a comparison.

The QT variability-related indices include but are not limited to the QT variability index proposed in (1) and NRR.

For the relationship between the RRI and QT interval, we consider the time-varying coupling index proposed in (14), which captures when RRI and QT interval share fixed oscillatory patterns. We call the assembly of all considered exposures an *extra-long-term dynamical vector*, which can be represented by a polar chart.

Outcomes
AF, CHD, and heart failure

Covariates
Age, sex, race/study center, occupation, educational level, smoking (never, former, current), alcohol intake, physical activity, body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, and use of medications (anticoagulants, aspirin, beta blockers, calcium channel blockers, and antiarrhythmic drugs).

Statistical analysis

Aims #1 & #2
We will model the extra-long-term dynamical vector as a continuous random vector.

We will use multivariable logistic regression to evaluate the association of the extra-long-term dynamical vector with outcomes, adjusting for covariates using the following models:

Model 1: Age, sex, race/study center, occupation, and educational level
Model 2: Model 1 + smoking, alcohol intake, physical activity, body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, and use of medications.

We will also test for sex- and race-based interactions and conduct sex- and race-stratified analyses.

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/mantrack/maintain/search/dtSearch.html

__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)?

#2433 (Norby)
#1998 (Chen)
#1913 (Chen)

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.

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