1.a. Full title: Correlates of Ultra-low frequency heart rate variability on 14-day ECG
1.b. Abbreviated title (26 char): Predictors of ULF HRV


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

First author: 
Name: Larisa G. Tereshchenko MD, PhD
Address: Oregon Health & Science University, Knight Cardiovascular Institute, 3181 SW Sam Jackson Park Rd UHN62 Portland, OR 97239 phone 503-494-2374 email: tereshch@ohsu.edu; lteresh1@jhmi.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: Josef Coresh
2020 E. Monument Street, Suite: Baltimore, MD, 21287 Email: jcoresh@jhsph.edu Phone: 410 955-0495 Phone; Fax: 410-955-0476

2. Timeline: Start – immediately after approval (expected, December 2013). Manuscript submission expected: 9 months

Rationale: 

*Ultra-low frequency heart rate variability.* Heart rate variability (HRV) was shown to be associated with cardiovascular death and arrhythmic events⁴. High frequency (HF) cyclic
fluctuations are modulated by breathing, mediated mostly by changes in vagal outflow. The greatest variation of RR’ intervals occurs with circadian changes (night-day variations), mediated by poorly understood neurohormonal rhythms. Most data on HRV is limited to few minutes to a maximum of 48h of continuous RR’ intervals. The physiologic mechanisms responsible for very low frequency (VLF, 0.0033-0.04Hz) and ultra-low frequency (ULF, <0.003 Hz) are matter of dispute. Data suggests influence of the renin-aldosterone system, thermoregulation, vasomotor activity, physical activity, and sleep-disordered breathing. In the Vietnam Era Twin Registry study a significant inverse correlation was found between depressive symptoms and ULF HRV. Association between cognitive impairment and ULF-VLF HRV in patients with dementia was reported. ULF and VLF HRV are associated with verbal learning and memory.

However, previous studies of ULF HRV were limited by the short data available (up to 48h), which did not allow to quantify ULF reliably. Consequently, it is also not clearly known whether ULF oscillations are determined by periodic or quasiperiodic oscillations of HRV that originates from body’s intrinsic regulatory system.

Recently for the first time in clinical practice FDA-approved long-term (up to 14 days) continuous ECG monitoring (ECG Zio-Patch, iRhythm, Inc.) became available. However, iRhythm’s (manufacturer of ECG Zio-Patch) does not measure heart rate variability.

Tereshchenko’s laboratory developed custom software application to measure HRV with the focus on ultra-low frequency pattern of variability.

Recently ARIC ZioPatch Ancillary Study (Agarwal, Chen, et al., proposal # 2013.14) successfully started and is currently ongoing. Overall 350 ZioPatch ECGs will be recorded and available for analysis. I plan to apply custom analysis to measure ULF HRV.

**Main hypothesis/Study questions:**

*Aim 1:* To describe ULF HRV in ARIC-NCS Stage III participants.

*Aim 2:* To describe correlates and associations of ULF HRV on 14-day ECG in ARIC-NCS Stage III participants.

We hypothesize that characteristics (volume, activity) of particular brain areas, as well as characteristics, localization and the size of brain lesions predict ULF HRV pattern.

**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).**

**Methods**
ECG signal will be analyzed using customized Matlab (MathWorks, Inc, Natick, MA) software. ULF HRV will be measured by custom Matlab software.

ARIC participants with available ECG Zio-Patch recording will be included (N=350).
We will conduct cross-sectional analyses to examine the association between ULF HRV with brain function. Log-transformed ULF HRV will serve as an outcome, as a continuous variable. Unadjusted and multivariable adjusted linear regressions models will be used. The associations of ULF HRV and each of the following variables will be examined in unadjusted models: brain MRI lesions characteristics (size and localization), neuroimaging measures of the brain regional volumes, loss of neurons as detected by neuroimaging, white matter integrity measured by DTI, structural brain mapping by VBM, brain amyloid burden measured by PET. Models will be adjusted by age, sex, race (model 1), hypertension, diabetes, BMI (model 2+1), physical activity (model 3+2), and medications (beta-blockers and central psychotropic drugs, such as antidepressants, tranquilizers, neuroleptics, barbiturates) (model 4+3).

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/or DNA analysis RES_DNA = “CVD Research” would be used? ____ Yes ____ No (This file ICTDER03 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/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)?

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 (______)
   ____ 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.c.unc.edu/aric/forms/

12. 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.
Reference List


