ARIC Manuscript Proposal # 3293

1.a. Full Title: Sex differences in association of global electrical heterogeneity with sudden cardiac death: The Atherosclerosis Risk in Communities (ARIC) study

  b. Abbreviated Title (Length 26 characters): **Sex, GEH, and SCD**

2.   Writing Group:
     Writing group members:
-Stacey Howell, MD, (design, background literature review, interpretation of results, writing)
-Erick A. Perez-Alday, PhD, Yin Li-Pershing, BS (Matlab software development and automated ECG analyses, interpretation of results)
-Aron Bender, MD, David German, MD, Tuan Mai, MD, Srini V. Mukundan, MD, (clinical adjudication of each cardiac beat origin and conduction path = beats labeling, interpretation of results)
-Christopher Hamilton, BA, Jason Thomas, BS, Nichole Rogovoy, BS, (quality control of ECG analyses, review of accuracy fiducial points, interpretation of results)
-Larisa G. Tereshchenko, MD, PhD (design, statistical analyses, oversight, interpretation of results, writing)

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. SH and LT_____ **[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: 2019

4.   Rationale:
     We recently showed that electrocardiographic global electrical heterogeneity (ECG-GEH), measured by five features of the spatial ventricular gradient (SVG) vector (SVG magnitude, direction (azimuth and elevation), a scalar value sum absolute QRST integral (SAI QRST), and

spatial QRS-T angle) on orthogonal XYZ ECG is associated with sudden cardiac death (SCD). In the pooled ARIC+CHS population,[1] we showed that 5 GEH measurements were independently associated with SCD after adjustment for demographics, manifested CV disease (time-updated incident non-fatal cardiovascular events [CHD, HF, stroke, AF, use of beta-blockers], and known CV risk factors such as total cholesterol, HDL, triglycerides, physical activity index, smoking, diabetes, BMI, hypertension, anti-hypertensive medications, creatinine, alcohol intake, LVEF, and time-updated ECG risk-factors (heart rate, QTc, QRS duration, ECG-LVH, bundle branch block [BBB] or interventricular conduction delay [IVCD]). GEH selectively predicted SCA over non-sudden fatal CHD and non-cardiac death in competing risks models, suggesting that abnormal GEH selectively identified participants with abnormal EP substrate rather than simply identifying a sicker population with structural heart disease.

Sex differences in SCD rate are well-known. However, mechanisms behind sex differences in SCD are not entirely clear. While SCD is less frequent in women, prediction of SCD in women is more challenging than in men. Recent Finnish study showed sex differences in GEH-association with fatal CVD.[2] However, it remains unknown whether sex modify association of GEH with SCD

5. Main Hypothesis/Study Questions:
We will test the hypothesis that sex is an effect modifier; it modifies association of ECG GEH phenotype with SCD.

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).

All ARIC participants with available and analyzable ECGs, who have GEH results reported (both area vectors[1] and peak vectors[3]) will be included.
We will test for interaction in a population of both men and women, in the described below analyses. Next, we will run stratified analyses in male and female subgroups.
We will use Cox proportional hazards and Fine and Gray competing risk models to study associations between each ECG predictor variable treated as continuous variable and SCD. To assess the independent association of GEH measures with SCD, we will adjust for other clinical factors that are known to be associated with SCD (such as time-updated CV disease (CHD, HF, stroke, AF), known CV risk factors, and known ECG predictors of SCD. Schoenfeld residuals will be studied to confirm that the proportional hazards assumption was valid in all Cox models. Circular statistics will be used to compare circular variables (SVG azimuth and elevation) in men and women.

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)? 2208

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* _2012.14___)
      ___ 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:

1.   Waks JW, Sitlani CM, Soliman EZ, Kabir M, Ghafoori E, Biggs ML, Henrikson CA, Sotoodehnia N, Biering-Sorensen T, Agarwal SK, Siscovick DS, Post WS, Solomon SD, Buxton AE, Josephson ME and Tereshchenko LG. Global Electric Heterogeneity Risk Score for Prediction of Sudden Cardiac Death in the General

Population: The Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) Studies. *Circulation*. 2016;133:2222-34.

2.   Lipponen JA, Kurl S and Laukkanen JA. Global electrical heterogeneity as a predictor of cardiovascular mortality in men and women. *EP Europace*. 2018:euy113-euy113.

3.   Erick Andres Perez-Alday YL-P, Aron Bender, Christopher Hamilton, Jason Thomas, Kyle Johnson, Tiffany L. Lee, Ryan Gonzales, Aaron Li, Kelley Newton, Larisa G. Tereshchenko. Importance of the Heart Vector Origin Point Definition for an ECG analysis: The Atherosclerosis Risk in Communities (ARIC) study. *Comput Biol Med*. 2018.