1.a. Full Title: Sex Differences in the Association of ECG Global Electrical Heterogeneity with Cardiac Structure and Function in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): sex, GEH, and LV systolic function

2. Writing Group:
   Writing group members:
   - Katie Lutz, MD (design, background literature review, ECG analysis/beat labeling, interpretation of results, writing)
   - Kazi Haq, PhD, (Matlab software development and automated ECG analyses, interpretation of results)
   - Stacey Howell, MD, (ECG analysis/beat labeling, interpretation of results)
   - Nichole Rogovoy, BS, (quality control of ECG analyses, review of accuracy fiducial points, interpretation of results)
   - Scott Solomon, MD, Amil M. Shah, MD, MPH, Tor Biering-Sørensen, MD, PhD, MPH (echocardiogram analyses, interpretation of results)
   - Larisa G. Tereshchenko, MD, PhD (design, beats labeling, statistical analyses, oversight, interpretation of results, writing)

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

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3. Timeline: 2020

4. Rationale:
In the United States, the annual incidence of sudden cardiac death (SCD) ranges between 180,000 to 450,000 cases.\(^1\) SCD survival rate is quite low, with only 8-10% of patients surviving to hospital discharge.\(^2\) Left ventricular dysfunction is one of the most common conditions that has the highest population attributable risk for sudden cardiac death at over 30%.\(^3\) Current practice of risk stratification for implantable cardioverter defibrillators (ICDs), the only current preventative measure for SCD, is based on left ventricular dysfunction. In one study, sudden death was the first manifestation of cardiac disease for more than half of their adult population of SCDs.\(^4\) Another review found approximately two-thirds of all SCDs caused by coronary heart disease occur either as the first clinical manifestation or in individuals who have been identified with coronary heart disease but have been identified as low risk based on current risk stratification.\(^5\) Data suggest the incidence of SCD is low in the general population, but the absolute number of events in the general population is actually higher than those who are high-risk for CAD. This discrepancy is due to the denominator of the general population being so large compared to those who have already had cardiac events.\(^5\) These data suggest improvement could be made for individual risk profiling to provide larger preventive benefits.

There are important sex differences in SCD. The National Health and Nutrition Examination Survey data suggests prevalence of cardiovascular disease for both males and females over 20 years of age is 48% overall, and increases with age in both sexes.\(^6\) The San Francisco POST SCD Study measured the autopsy-defined sudden arrhythmic death (SAD) in individuals with sudden cardiac death and found that SAD accounted for 61% of SCD in men, but only 45% in women.\(^4\) Women with SCD are more likely to present with pulseless electrical activity or asystole compared to males, which both have a significantly lower rate of successful resuscitation.\(^7\) Women are less likely than men to have a diagnosis of structural heart disease prior to sudden cardiac arrest, suggesting that fewer women are eligible for prophylactic ICD placement.\(^7\) Mechanisms of SCD are incompletely understood, and these statistics suggest that the current practice of risk stratification of SCD based on left ventricular dysfunction is inadequate.

It is known that men and women have differences in cardiac structure, function, and electrophysiological substrate. Men have more eccentric remodeling as well as greater values of left ventricular (LV) mass, wall thickness, and cavity dimensions at all ages. Women have more accelerated increases in LV wall thickness following menopause and more age-related concentric modeling.\(^8\) Men have an earlier onset of impaired systolic performance, while women have a later onset of impaired systolic performance, greater impairment in diastolic function, and greater age-related increases in ejection fraction.\(^8\) These differences have been hypothesized to be due to an increased pulsatile load in post-menopausal women, differential gene expression in pressure overloaded states, and withdrawal of estrogens at the time of menopause.\(^8\) The effect of sex on global longitudinal strain (GLS), which provides prognosis for heart failure related outcomes independent of left ventricular ejection fraction, is controversial; overall, women have been observed to have increased GLS, particularly in the pre-menopause ages.\(^9\) Women also have a faster heart rate, narrower QRS, and longer QT interval compared to men.\(^10\) ECG is one of the most inexpensive and widely available modalities to measure risk stratification of sudden cardiac death. ECG measurement can be expanded upon by utilizing global electrical heterogeneity (GEH), which characterizes the degree of heterogeneity in the total recovery time across the ventricles.\(^11\) GEH is quantified by spatial ventricular gradient (SVG) magnitude and direction (elevation and azimuth), scalar value sum absolute QRST integral (SAI QRST), and spatial QRS-T angle.\(^11\) The larger the degree of heterogeneity, the larger the SVG magnitude, and
the SVG vector points toward the area where the recovery time is the shortest. One study has developed a novel, highly specific SCD risk score using GEH parameters that has the potential to be used along with clinical-only SCD. Slowly worsening GEH parameters over time are associated with subsequent LV dysfunction, while rapidly worsening GEH parameters are associated with SCD. Additionally, longitudinally increasing QRS-T angle, SAI QRST, and changing SVG direction were strongly associated with LV systolic dysfunction. A study examined GEH independent risk factors for cardiovascular mortality and found the significant factors in men were abnormal QRS-T angle and QTc interval, while in women abnormal QRS-T angle and SAI QRST were significant. Another study has suggested that the sex differences in SVG magnitude can be explained by differences in body size and multiple clinical factors including heart failure, stroke, diabetes, BMI, and hypertension. However, this same study has shown that global electrophysiological substrate, including heart rate, QTc, QRS duration, Cornell voltage, SAI QRST, and SVG magnitude, is associated with up to 27% greater risk of SCD in women compared to men. It remains unknown if sex is an effect modifier of the association of GEH ECG phenotype with LV structure and function. The results of this study could help understand underlying mechanisms of SCD and assist with SCD risk stratification.

5. Main Hypothesis/Study Questions:
We hypothesize that sex is an effect modifier of cross-sectional and longitudinal association of GEH ECG phenotype with LV structure and function.

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 and echocardiogram (both at visit 5), who have GEH results reported (both area vectors and peak vectors) will be included. We will exclude Black participants in the Washington and Minnesota cohorts and participants with reported race other than white or black, and participants with missing covariates. GEH ECG phenotype will be assessed using SVG magnitude and direction (azimuth and elevation), SAI QRST, and spatial QRS-T angle. For comparison, traditional global ECG metrics will be included (QTc, QRS duration, and Cornell voltage). LV function will be assessed using continuous variables (LVEF, GLS, LVESVi, LVEDVi, LVMi) and binary abnormal LV function using cutoffs known to be different for men and women. For assessment of left ventricular structure and function, at least one abnormal value of left ventricular structure and function will be considered abnormal for both the cross-sectional analysis and longitudinal analysis. ARIC-specific thresholds for abnormal LV structure and function will be used in this study: LVEF based on ARIC reference limits (<57.4% in women or <59.0% in men), LV enlargement based on left ventricular end-diastolic volume (LVEDV) indexed to body surface area (BSA) above ARIC reference limits (>51.9 mL/m2 in women or >60.2 mL/m2 in men), LV end-systolic volume index (LVESVi) > 31 mL/m2 for men and > 24 mL/m2 for women, left ventricular hypertrophy based on ARIC reference limits for LV mass indexed to height (>) in
women or >45.0 g/m2.7 in men); global longitudinal strain (GLS) <15.2% and <14.7% in women and men, respectively.

**Cross-sectional Analyses**
Data from Visit 5 will be used for cross-sectional analyses of GEH ECG phenotype and LV structure and function. Individuals will be excluded if echocardiogram was not obtained at visit 5. ECG continuous variables (GEH, QTc, QRS, Cornell voltage) will serve as predictor variables. Echocardiographic metrics of cardiac structure and function (LVEF, GLS, LVEDVi, LVESVi, LVMi) will serve as outcome continuous variables. Linear regression models will adjust for age, race, and known confounders of cardiac structure (prevalent at visit 5 CHD, HF, hypertension, diabetes, body mass index, smoking, presence of ventricular conduction abnormalities, and heart rate and systolic and diastolic blood pressure measured at the time of echocardiography). The interaction term of sex*ECG variable will be added into each model.

**Longitudinal Analyses**
Data from Visits 1-5 will be used for longitudinal analyses of GEH ECG phenotype in two subgroups of participants with and without abnormal systolic LV function (per thresholds listed above). Participants will be placed in groups that describe the trajectory of GEH ECG phenotype over time. Population-averaged (GEE) and patient-specific (Mixed with random effect) models will be used. The interaction term of sex*ECG variable will be added into each model. The first model will have minimal adjustment for age and demographics. The second model will adjust for both prevalent disease and risk factors including smoking status, physical activity, lipids, hypertension, and diabetes. The goal of regression modeling is to find out whether man and women with normal vs. abnormal LV structure and function experienced different longitudinal trajectories in ECG-GEH changes, and whether longitudinal association of electrical substrate (GEH and traditional global ECG measures) with LV structure and function are explained by prevalent and presumably subclinical CVD / CVD risk factors, and whether sex modify an independent association (in fully adjusted model).

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 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  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:


