1.a. Full Title: Longitudinal association of global electrical heterogeneity with lipids: The Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): GEH and lipids

2. Writing Group:

   Writing group members:
   - Katherine Yang, BS, (background literature review, interpretation of results, writing, design)
   - Erick A. Perez-Alday, PhD, Kazi Haq, PhD (Matlab software development and automated ECG analyses, interpretation of results)
   - Aron Bender, MD, David German, MD, Srini V. Mukundan, MD, Stacey Howard, MD, (clinical adjudication of each cardiac beat origin and conduction path = beats labeling, interpretation of results)
   - Christopher Hamilton, BA, Nichole Rogovoy, BS, Jason Thomas, BS (quality control of ECG analyses, review of accuracy fiducial points, 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. KY and LT______ [please confirm with your initials electronically or in writing]

   First author: Katherine Yang (Penn State and Sidney Kimmel Medical College 7 year accelerated premedical-medical B.S./M.D. program student; visiting intern in Tereshchenko lab)
   Address: 3181 SW Sam Jackson Park Rd, UHN62; Portland, OR 97239
   Phone 503-494-2374; Fax 503-494-8550
   E-mail: kqy5107@psu.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: Larisa Tereshchenko, MD, PhD
   Address: 3181 SW Sam Jackson Park Rd, UHN62; Portland, OR 97239
   Phone 503-494-2374; Fax 503-494-8550
   E-mail: tereshch@ohsu.edu

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), its 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, 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. GEH selectively predicted SCD 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.

Coronary heart disease (CHD) is a well-known and the most widely prevalent in population substrate of SCD. In our previous study we observed cross-sectional association of GEH with prevalent CHD. However, longitudinal associations between GEH phenotype and known risk factors of CHD (lipids: LDL, HDL, total cholesterol, triglycerides) are unknown. As GEH phenotype can be easily measured on 12-lead ECG, if GEH phenotype is sensitive enough to detect favorable (or non-favorable/insufficient) changes in lipids in response to lipid-lowering treatment, GEH phenotype can be used to monitor effect of lipid-lowering treatment on the risk of SCD. Currently, there is no strong data to support direct effect of statins on the risk of SCD. Obviously, indirect effect (via reduction of CHD incidence – reduction of myocardial infarctions/patchy scar) is undisputable.

It is known that the most widely used lipid-lowering drugs (statins) leave residual risk of CHD development, e.g statins do not normalize the level of triglycerides. In turn, triglycerides hypothetically can infiltrate myocardium (fat infiltration), promote proinflammatory response (known as metabolic syndrome) and facilitate development of interstitial fibrosis (independently from development of coronary atherosclerosis). Interstitial fibrosis is a well-known arrhythmogenic substrate. Hypothetically, lipids can act on two pathways: (1) via development of coronary atherosclerosis, which can be prevented by statins, affecting mostly LDL); (2) via hypertriglyceridemia, leading to fat infiltration, which activates inflammatory response, and finally result in an interstitial fibrosis. ARIC cohort is a unique cohort that collected longitudinal data on lipids level (HDL, LDL, triglycerides), and use of lipid-lowering drugs, as well as carefully adjudicated incident CHD. Thus, we will be able to dissect possible causal pathways as hypothesized above, using causal mediation and causal inference analyses.

We designed this study to investigate longitudinal (possibly causative) associations between longitudinal changes in lipids (total cholesterol, LDL, HDL, triglycerides), use of lipid-lowering drugs (statins), and GEH phenotype.

5. Main Hypothesis/Study Questions:
We hypothesize that the level of triglycerides (but not LDL/HDL/total cholesterol) and use of lipid-lowering medications is independently (after adjustment for incident CHD) associated with GEH phenotype in longitudinal analysis. We further hypothesize that the use of lipid-lowering medications mediates the longitudinal effect of lipids (total cholesterol, LDL, HDL, triglycerides) on GEH phenotype. We also hypothesized that the levels of LDL/HDL/total cholesterol are associated with GEH phenotype in minimally adjusted analyses, but this association is fully explained by incident CHD events.
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\(^5\)) will be included. We will exclude participants without lipids (total cholesterol, LDL, HDL, triglycerides) data, participants with race other than black or white, and black participants in MN and Washington county (MD).

Mixed regression models\(^6\) will be used. In order to determine whether the patient-specific time-varying changes in the specific lipid level are associated with the patient-specific time-varying GEH changes, we will conduct generalized least squares random-effects linear regression analysis. First, patient-specific time-varying ECG variables (continuous variables, each in separate models set) will serve as an outcome. Patient-specific time-varying lipid level will serve as a predictor. We will perform Hausman test to choose between the random-effect estimator (assuming that the unobserved time-invariant random component is unrelated to the predictors) and fixed-effect estimator (allowing the unobserved random component to be related to the predictors). We will adjust for confounding demographic variables and known CVD risk factors. Longitudinal analyses will be conducted in a structural equation modeling\(^7\) framework. Lipids level measured at visit 1 will serve as predictor of GEH at visit 2. Lipids level measured at visit 2 will serve as a predictor of GEH at visit 3. There will be no cross-sectional associations included; longitudinal only. In addition, we will conduct causal mediation analysis, and causal inference analysis (as developed by Jamie Robins). In causal mediation analysis, use of lipid-lowering drug is exposure, a lipid level (or incident CHD event) is a mediator, and GEH is an outcome. Causal medication analysis will answer a question whether the use of a statin affect GEH phenotype, and whether an effect of a medication is direct or is mediated (by lipids level or by incident CHD event).

Circular variables analyses: Spatial QRS-T angle, SVG azimuth, and SVG elevation are circular variables. By convention, QRS-T and SVG elevation angles can be only positive, ranging from 0 to 180 degrees. Distributions of QRS-T angle and SVG elevation angle were normal, or nearly normal. Thus, QRS-T and SVG elevation angles were included in all conventional statistical analyses without transformation. SVG azimuth angle is expressed as axial variable, ranging from -180° to +180°. We transformed SVG azimuth by doubling its value, and then reducing it modulo 360° (i.e. adding 360°). Then we analysed the SVG azimuth using conventional statistical approach, and for interpretation we transformed it back.

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: