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

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

2. **Writing Group:**
   Writing group members:
   - Ashley Wirth, 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. AW and LT_____ [please confirm with your initials electronically or in writing]

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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), 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,\(^1\) 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. 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.

Diabetes is a well-known risk factor for both micro- and macro-vascular heart disease. Multiple studies have recently established that hypoglycemia and hyperglycemia may have important implications for the development of arrhythmias. Gill et al\(^2\) examined 25 type I diabetics with ECG monitoring over a 5-day time interval and found substantial cardiac rate/rhythm disturbances during episodes of nocturnal hypoglycemia that offered support for the idea of “dead in bed” syndrome in which Type I Diabetics experienced nocturnal sudden cardiac death without a clear etiology. Stahn et al\(^3\) and Chow et al\(^4\) examined ECG data over 5-day time intervals correlated with continuous glucose monitoring data in Type 2 Diabetics and found substantial evidence of heart rate variability and various arrhythmias that occurred during distinct episodes of hypoglycemia.

In our previous study of SCD in ARIC, diabetes was predictive of SCD, and included in the risk score of SCD.\(^1\) In another study of ARIC, Kucharska-Newton et al showed that diabetes is associated with both SCD and non-sudden cardiac death, suggesting that diabetes does not confer a specific excess risk of SCD.\(^5\) We previously showed that diabetes is strengthening cross-sectional association of some GEH metrics with left ventricular systolic function measured on echocardiogram. Interestingly, interaction with diabetes status was observed only for amplitude-based ECG metrics (SAI QRST, Cornell voltage, SVG magnitude) and QTc, but no interaction with diabetes was found for QRS-T angle and SVG direction. Moreover, another intriguing finding was a genome-wide association of a GEH phenotype (SAI QRST) with genetic polymorphism in the intron of the insulin-like growth factor 1 (IGF1)-Receptor (IGF1R) gene.\(^6\) The same SNP as identified in our GEH GWAS was previously reported associated with fasting glucose level, but not diabetes. As GEH phenotype can be easily monitored on 12-lead ECG, it would be beneficial to understand dynamic associations of diabetes status, glucose level, insulin level, and GEH phenotype. If such longitudinal associations exist, GEH can be possibly used to monitor effect of glucose-lowering interventions on electrophysiological substrate. Moreover, future mendelian randomization analysis can possibly help to understand one of mechanisms behind GEH.

In a subgroup of patients with diagnosed diabetes, we will conduct causal inference analysis. Diabetes treatment will serve as exposure, glucose/insulin level will serve as a mediator, and GEH phenotype is an outcome. Causal mediation analysis will answer a question whether and to what degree effect of glucose-lowering medication on GEH phenotype is mediated by the level of glucose/insulin, or it is direct (independent from glucose/insulin level).

5. **Main Hypothesis/Study Questions:**
We hypothesize that diabetes status, glucose level, and insulin level is associated with GEH phenotype in longitudinal analysis.

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 and peak vectors) will be included. We will exclude participants without diabetes status data (fasting and non-fasting glucose level, insulin level) at baseline only, participants with race other than black or white, and black participants in MN and Washington county (MD). We will use multiple imputations by the chained equations (MICE) method to account for attrition, similarly to that described in. Validation of the MICE approach in ARIC has been previously reported and it has been determined that MICE produced unbiased imputed values. As a sensitivity analysis, we will completely exclude participants with missing diabetes data (at baseline and any followup visit).

Mixed regression models will be used. In order to determine whether the patient-specific time-varying changes in the glucose, insulin level, and diabetes status 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 glucose/insulin level or binary diabetes status (yes/no) 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 framework. Diabetes status assessed at visit 1 will serve as predictor of GEH at visit 2. Diabetes status assessed at visit 2 will serve as a predictor of GEH at visit 3. In this exploratory analysis, both cross-sectional associations and longitudinal associations will be studied.

In a subgroup of patients with diagnosed diabetes, we will conduct causal inference analysis. Diabetes treatment will serve as exposure, glucose/insulin level will serve as a mediator, and GEH phenotype is an outcome.

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 are normal, or nearly normal. Thus, QRS-T and SVG elevation angles are included in all conventional statistical analyses without transformation. SVG azimuth angle is expressed as axial variable, ranging from -180° to +180°. We transform SVG azimuth by doubling its value, and then reduce it modulo 360° (i.e. adding 360°). Then we analyze the SVG azimuth using conventional statistical approach, and for interpretation we transform it back.

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.cscce.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.cscce.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:


