1.a. Full Title: Association of global electrical heterogeneity with incident coronary heart disease: The Atherosclerosis Risk in Communities (ARIC) study

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

2. Writing Group:
   Writing group members:
   - Francis Phan, 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, 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, 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. FP 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, 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.

Coronary heart disease (CHD) is a well-known and the most frequent in the general population substrate of SCD. In our previous work, we did not find significant statistical interaction of the CHD status with association of GEH with SCD, suggesting no difference in association of GEH with SCD in individuals with vs. without CHD. However, dynamic relationships between GEH, incident CHD, and SCD are unknown. Some individuals first develop (are diagnosed with) CHD and later succumb to SCD. In other individuals SCD can be the first manifestation of cardiovascular disease. Our long-term goal is development of dynamic risk score of SCD, which will account for the timing of incident cardiovascular events (including incident CHD). In this study, in preparation to the development of dynamic SCD risk score we are planning to investigate whether GEH is independently associated with incident CHD.

Previous studies reported association of frontal and spatial QRS-T angle with incident CHD in ARIC. However, it is unknown how all GEH metrics are associated with CHD. From pathophysiological point of view, at the current state of knowledge, there is no data that suggest any specific mechanism behind possible association of GEH with incident CHD. The only explanation of such association could be that GEH can possibly detect asymptomatic CHD early, before its clinical manifestation. Therefore, we hypothesize that GEH is associated with incident CHD. However, such association is likely fully explained by known CHD risk factors.

5. Main Hypothesis/Study Questions:
We hypothesize that ECG GEH phenotype is associated with incident CHD.

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 Black participants in the Washington and Minnesota cohorts and participants with reported race other than white or black, and participants with missing covariates, and participants with prevalent at visit 1 CHD.

Cox regression analyses will be conducted with incident CHD as primary outcome. Incident CHD is defined as a composite of incident myocardial infarction (MI), silent MI, revascularization procedure, angina, or a fatal CHD. Incident definite and probable MI was classified on the basis of the following: (i) an evolving diagnostic ECG pattern (as determined by the Minnesota Code); (ii) a diagnostic ECG pattern and abnormal cardiac biomarkers; or (iii)
cardiac pain with abnormal cardiac biomarkers and either evolving ST-T wave changes on ECG or an equivocal ECG pattern. Separate components of incident CHD will serve as secondary outcomes.

We will conduct survival analysis. We will construct several Cox regression models with the goal to determine whether association of GEH with incident CHD is independent from subclinical coronary heart disease (CHD’s risk factors). Model 1 is adjusted for demographic characteristics (age, sex, race, and study center). Model 2 is in addition adjusted for prevalent PAD, AF, stroke, heart failure (HF), use of β-blockers, eGFR_{CKD-EPI}, body mass index, hypertension, antihypertensive medications, diabetes mellitus, smoking status, alcohol intake, total cholesterol, high density lipoprotein cholesterol, triglycerides, and physical activity index, and education). Model 3 further adjusted for electrocardiographic parameters associated with CHD (heart rate, QRS, QTc duration, sex-specific Cornell product, and bundle-branch block, or intraventricular conduction delay). Model 4 evaluate whether the association of GEH parameters with CHD remained significant over time and included all baseline covariates included in model 3, time-updated GEH parameters, time-updated traditional electrocardiographic measurements, and time-updated incident other cardiovascular events (AF, PAD, HF, and stroke). Schoenfeld residuals will be used to confirm that the proportional hazards assumption is valid in all Cox proportional hazards models. Circular statistics will be used to analyze circular variable (SVG azimuth).

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 ___ X__ 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 ___ X__ 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:


