ARIC Manuscript Proposal # 3333

PC Reviewed: 1/8/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

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

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

2. Writing Group:

Writing group members:

-Deanna Green, 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. DG 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.

Stroke is well-known risk factor of SCD.(1) However, dynamic relationships between GEH, incident stroke, and SCD are unknown. Some individuals first develop incident stroke 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 stroke). 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 stroke. There were no previous studies of association of GEH or its component (QRS-T angle) with incident stroke. There are at least two potential mechanisms that can explain possible association of GEH with incident stroke. First, GEH can serve as a marker of structural heart disease, and it is known that structural heart disease is a risk factor of stroke, via common mechanisms affecting endothelial function. Second mechanism can explain a hypothetical association of GEH with thromboembolic stroke, as GEH reflects cardiac memory, and, therefore, reflects burden of asymptomatic ventricular arrhythmias (PVCs). Association of premature ventricular complexes (PVCs) with incident stroke in ARIC has been demonstrated.(2) Study of association of GEH with incident stroke will help to understand underlying mechanisms, and will serve for preparation for future development of the dynamic risk score of SCD.

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

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 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 stroke.

In ARIC incident stroke(4) was adjudicated by physicians-reviewers, and by computerized algorithm. Both definite and probable stroke cases will serve as a primary outcome. Stroke subtypes (hemorrhagic (including subarachnoid hemorrhage), non-carotid embolic, and thrombotic stroke) will serve as secondary outcomes.

Cox regression analyses will be conducted with incident stroke as primary outcome, and with secondary outcomes. We will construct several models with the goal to determine whether association of GEH with incident stroke is independent from cardiovascular disease (and its risk factors). Model 1 is adjusted for demographic characteristics (age, sex, race, and study center). Model 2 is in addition adjusted for prevalent CHD and its risk factors (CHD, AF, stroke, use of β-blockers, creatinine, body mass index, hypertension, antihypertensive medications, diabetes mellitus, smoking status, alcohol intake, total cholesterol, high density lipoprotein cholesterol, triglycerides, physical activity index, and education). Model 3 further adjusted for electrocardiographic parameters associated with stroke (heart rate, PR interval, QRS, QTc duration, sex-specific Cornell product, and bundle-branch block, or intraventricular conduction delay). Model 4 evaluated whether the association of GEH parameters with stroke 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 nonfatal cardiovascular events (AF, CHD, and HF). 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 variables (SVG azimuth and elevation).

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:

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2. Agarwal SK, Heiss G, Rautaharju PM, Shahar E, Massing MW, Simpson RJ, Jr. Premature ventricular complexes and the risk of incident stroke: the Atherosclerosis Risk In Communities (ARIC) Study. Stroke. 2010;41(4):588-93. Epub 2010/02/20. doi: 10.1161/STROKEAHA.109.567800. PubMed PMID: 20167922; PMCID: PMC2866170.
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.
4. Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, Copper LS, Shahar E. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke. 1999;30(4):736-43.