1.a. **Full Title:** Initial direction of ventricular activation in early repolarization, and its association with sudden cardiac death: The atherosclerosis in risk communities (ARIC) study.

b. **Abbreviated Title (Length 26 characters):**

2. **Writing Group:**
   - Katherine Yang, BS, (background literature review, Matlab software development and automated ECG analyses, interpretation of results, writing, design)
   - Kazi Haq, PhD (participation in Matlab software development and automated ECG analyses, interpretation of results)
   - Stacey Howard, MD, 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)
   - 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. KY and LT____ [please confirm with your initials electronically or in writing]

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3. **Timeline:** 2019

4. **Rationale:**
Early repolarization is a pattern commonly observed in electrocardiograms, presenting as a notch or slur at the end of the QRS complex called the J-wave. This type of ECG morphology can be generally described as J-point elevation. Occurring in anywhere from 2-31% of ECGs, this pattern’s broad range of estimated prevalence can be attributed to a lack of consensus regarding the precise definition of the phenomenon itself. Furthermore, the exact mechanism of the phenomenon is not well understood, although there are some indications that there are various genetic components. There is a controversy whether a J-wave elevation is a manifestation of an underlying feature of repolarization or depolarization. Despite the fact that the terminology of “early repolarization” has been in use by cardiologists for approximately 50 years, it remains poorly understood.

For many years, J-point elevation was considered a benign ECG pattern; however, recent studies have reached conflicting conclusions about its clinical importance. A 2008 study determined that early repolarization occurs more frequently in patients with idiopathic ventricular fibrillation than those in the control group, establishing an association between presence of J-waves and sudden cardiac death. The ARIC study on J-point elevation by Olson et al. concluded that there was a link to increased risk of sudden cardiac death for whites and females but not for blacks and males. While these studies establish that there is a clinical implication for J-point elevation and that it is not simply a benign pattern, they fail to determine the mechanism by which this occurs. Furthermore, Olson et al. suggest that J-point elevation may not uniformly increase risk for all patients, but that it may only put certain subgroups of patients at risk for sudden cardiac death.

In a recent athlete vectorcardiogram (VCG) study, we observed a case (see Figure at the end of this proposal) with a classical early repolarization ECG pattern paired with a vectorcardiographic ventricular activation pattern that appeared anomalous. In this case, the spatial vectorcardiogram demonstrated that the propagation of the QRS was initially to the patient’s posterior. This specific QRS activation differs from the more commonly observed pattern of an activation in the direction of the subject’s anterior. Such VCG presentation can be due to concealed septal activation. Consistently, there was complete absence of the q-wave and an abrupt upstroke of a narrow QRS complex on 12-lead ECG. Review of VCG morphology clearly demonstrated that a “J-wave” in V4-V6 and QRS slurring in II, III, and aVF corresponds to a QRS loop and not the repolarization phase. Direction of the QRS vector at the time of a “J-wave” is consistent with a normal pattern of ventricular activation of inferoposterior LV and RV outflow tract, as expected at the second half of QRS. This subject’s unusual pattern of ventricular activation was observed in the beginning and not the end of QRS. In this individual, activation spreads very fast in all directions in the LV, likely simultaneously towards the endo- and epicardium, which formed the initial QRS vector pointing backward, leftward, and downward, forming a narrow, abrupt QRS with concealed septal activation. We speculate that increased trabeculation of the subendocardium may allow the Purkinje network to more rapidly conduct through theoretically more porous LV walls, thus offering an explanation for the observed phenomenon. John P. Boineau previously described ER with narrow QRS complexes and discussed possible mechanisms. This case is of interest because this combination of VCG features is unlikely to be due to underlying factors such as a history of myocardial infarction; it may point to a subgroup of individuals with J-point elevation that is of interest. However, it remains unknown whether these individuals with specific activation with or without J-point elevation are in actually at higher risk of SCD.
5. **Main Hypothesis/Study Questions:**
We hypothesize that individuals with specific ventricular activation pattern (as described above) may represent a specific subgroup of individuals with J-point elevation (early repolarization ECG phenotype) that is associated with sudden cardiac death in the ARIC study population.

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 will be included. Participants with bundle branch block, diagnosed MI (including silent MI) will be excluded, because septal scar can be the cause of abnormal initial ventricular activation. We will also exclude participants who are not black or white, black participants in the Washington and Minnesota counties, and participants with missing covariates.

   Raw ECG data will be adjudicated. Spatial vectorcardiograms (VCGs) will be constructed from available ECGs using previously developed custom MATLAB software. Kors transformation will be utilized to transform the 12-lead ECG signal into XYZ orthogonal leads. Following this, a median sinus beat will be constructed utilizing only normal sinus beats that are not distorted by artifact and not before and after premature ventricular and atrial complexes. For vectorcardiogram construction, the origin point is defined at the point at which the heart vector is electrically silent and not moving in 3-dimensional space. The constructed vectorcardiogram will then be analyzed for QRS activation.

   QRS activation direction will also be assessed utilizing custom MATLAB software; the first 20 ms of ventricular activation will be analyzed. The determination of posterior or anterior directionality is determined in the XZ-plane. Azimuth angle values provide information about directionality in this plane. An arctangent calculation with range -180 to 180 will be used to calculate these azimuth measures to preserve the directionality of the vectors. In order to capture the subgroup with the specific ventricular activation pattern of interest with the highest sensitivity, the azimuth value of vector average of the first 20 ms will be compared to that of the first vector. Based on these values, the determination of the direction of this initial QRS activation will be made.

   Once these cases of posterior ventricular activation are found, electrocardiogram analysis will be performed to determine which of these cases exhibit J-point elevation as defined by Macfarlane et al. At the end of ECG and VCG analysis, we will define the following exposure groups: (1) peculiar initial ventricular activation with J-point elevation (early repolarization pattern); (2) peculiar initial ventricular activation without J-point elevation (early repolarization pattern).

   We will conduct survival analysis, using Cox and competing risk regressions. SCD is the primary outcome, defined as previously. Non-SCD, and non-cardiac death will serve as competing outcomes in a Fine and Gray competing risk model.

   We will construct several models with the goal to determine whether association of the peculiar initial ventricular activation (with or without J-point elevation) with SCD is independent from structural heart disease (CVD 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...
CVD and its risk factors (CHD, HF, 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, and physical activity index). Model 3 further adjusted for electrocardiographic parameters associated with SCD (heart rate, QRS, QTc duration, sex-specific Cornell voltage). Model 4 evaluated whether the association of ECG parameters remained significant over time and included all baseline covariates included in model 3, time-updated ECG parameters, time-updated traditional electrocardiographic measurements, and time-updated incident nonfatal cardiovascular events (AF, HF, CHD, and stroke). Schoenfeld residuals will be used to confirm that the proportional hazards assumption is valid in all Cox proportional hazards models.

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](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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.

References:
