ARIC Manuscript Proposal #

PC Reviewed: ___/___/11                Status: _____               Priority: ____
SC Reviewed: __________               Status: _____               Priority: ____

1.a. Full Title: The association of re-polarization abnormalities with risk of sudden death in African American Participants of ARIC

b. Abbreviated Title (Length 26 characters): Re-polarization Abnormalities and Sudden Death in African Americans

2. Writing Group:
Writing group members: Saman Nazarian, Yiyi Zhang, Moyses Szklo, Joe Coresh, Brian Caffo, Gordon Tomaselli, Alvaro Alonso, Elsayed Soliman, Wendy Post, Eliseo Guallar

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _SN_ [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: Analyses will begin immediately after approval. The study is expected to be submitted for publication within the next 6 months.

4. Rationale: The presence of QRS-ST segment elevation in leads other than V1-3 on 12-lead electrocardiography has been associated with increased risk of death from cardiac causes. $^{1,2}$ The prevalence of ST segment elevation is significantly elevated in the African
American (14.6% of African Americans versus 5.8% of Caucasians) population.\(^3\) However, the predictive value of early re-polarization in the African American population has not been established.

5. **Main Hypothesis/Study Questions**: To define the magnitude (if any) of the association between re-polarization abnormalities on 12-lead ECG and sudden death in African American participants of ARIC.

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).

   a. **Study design** – Population based prospective cohort study
   
   b. **Participants** – African American and Caucasian participants of ARIC
   
   c. **Protocol and Data Analysis** – ECG and survival data on ARIC participants (African American and Caucasian) will be requested after obtaining approval. Hazard ratios and 95% confidence intervals for mortality and cardiac mortality in participants of ARIC with and without ST segment elevation will be calculated with Cox proportional hazards models. The results will be stratified by ethnicity. Multivariate models will include age, sex, systolic blood pressure, body-mass index, heart rate, sex, smoking status, and presence or absence of signs of left ventricular hypertrophy or coronary artery disease. Kaplan–Meier survival curves will be plotted (for the entire cohort and for African American participants) after stratification of participants by the presence or absence of early re-polarization and compared by means of the log-rank test.

   f. **Sample Size for Primary Outcome Variable** – Tikkanen and colleagues studied the ECGs of 10,957 participants in Finland’s Social Insurance Institution’s Coronary Heart Disease Study. Of all subjects 5.8% had evidence of re-polarization abnormality. The presence of re-polarization abnormalities imparted an increased risk of death, RR 1.28. The presence of repolarization abnormalities in African American participants of ARIC has previously been established at 14.6%.\(^3\) Assuming a RR of 1.28, median control survival time of 30 years, accrual time of 2 years, and follow-up time of 20 years, with control to case ratio of 5.7, a sample size of 437 cases will be needed (2993 total participants African American Participants). The expected sample size has not been
calculated for Caucasians since the primary focus will be on African American participants.

**g. Feasibility of Meeting Enrollment Goals** – If the African American Population in ARIC is less than the required sample size, efforts will be made to include participants from MESA and other community based studies.

**h. Limitations** – We will be unable to establish causal relationships. Depending upon the availability of clinical variables of interest, interactions with pre-existing conditions such as left ventricular hypertrophy will be explored, but will be limited in scope.

**i. Expected Results and Possibility of Negative Results** – We expect to find a high prevalence of re-polarization abnormalities in African American participants. It is possible that similar to previous findings, an elevated risk of sudden death will be associated with baseline re-polarization abnormalities. Negative results, however, would be equally important given the high prevalence of re-polarization abnormalities in African American individuals.

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 ICTDER03 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/search.php

   ____✓__ 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)?

   The only related manuscript is: 1/16/01 - #766: Primary repolarization abnormalities and the risk of incident cardiac events: The Atherosclerosis Risk in Communities Study (ARIC) – However, proposal #766 does not focus on African American participants. Additionally, the repolarization focus of the manuscript was T-wave axis.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ____ Yes  _✓_ No

11.b. If yes, is the proposal
   ____ A. primarily the result of an ancillary study (list number* __________)
   ____ 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 http://www.cscc.unc.edu/aric/forms/

12. 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.

References

