1.a. Full Title: Association of Abnormal P-Wave Axis with sudden cardiac death

b. Abbreviated Title (Length 26 characters): aPWA and SCD

2. Writing Group:

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AM__ [please confirm with your initials electronically or in writing]

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3. **Timeline:**
   - Statistical Analysis: 1 month
   - Manuscript Preparation: 2 months

4. **Rationale:**
   Sudden cardiac death (SCD) is a major public health concern in the United States with an estimated annual incidence of 250,000-300,000 cases.\(^1\) The vast majority of SCDs occur in individuals with subclinical but significant coronary heart disease (CHD) from the general population.\(^2\) The current paradigm for non-invasive SCD risk stratification is dependent on assessment of left ventricular ejection fraction (LVEF). This strategy has proved to be neither sensitive nor specific highlighting the need for non-invasive SCD predictors capable of identifying at-risk individuals in the general population earlier in the natural history of their underlying heart disease.\(^5,9\)

P-wave axis (PWA) is a routine measure on 12-lead ECGs that reflects the net vector component of atrial depolarization in the frontal plane. Abnormal P-wave axis (aPWA) is defined as any value outside 0-75 degrees. It has been linked to incident atrial fibrillation (AF) in the Cardiovascular Health Study (CHS) and all-cause mortality in the National Health and Nutrition Examination Survey (NHANES)\(^10,11\) but has not been linked to SCD. Of note, AF is independently associated with an increased risk of SCD in the general population\(^12\) and markers of left atrial abnormality that predict incident AF, specifically abnormal p-wave terminal force in V1 (PTFV1), are also independently associated with increased SCD risk in the general population. As opposed to abnormal PTFV1, aPWA is routinely reported on 12-lead ECGs. We hypothesized that aPWA is independently associated with SCD in the general population.

5. **Main Hypothesis/Study Questions:**

**AIM:**
Evaluate the association of aPWA with and SCD

**Hypothesis:**
aPWA will be independently associated with an increased risk of SCD.

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).**

**Study Population:**
We will include all participants at the baseline visit (V1). We will exclude those with missing covariates and missing ECG data.

**Exposure**
Normal P-wave axis will be defined as a value between 0 and 75 degrees. Abnormal P-wave axis (aPWA) will be defined as P-wave axis with values outside this window.

**Outcome**
SCD: In ARIC, all CHD deaths that occurred by December 31, 2001 were viewed by a panel of 5 physicians to identify SCD events. Each event was independently adjudicated
by 2 physicians. SCD was defined as death from a sudden pulseless condition presumed to be of cardiac origin in a previously stable individual without evidence of non-cardiac cause of death. All deaths classified as SCD had to occur outside of the hospital or in the emergency room. If there was a disagreement, a third investigator reviewed the event to provide final classification. After review of available data, CHD deaths were classified as definite sudden arrhythmic death, possible sudden arrhythmic death, not sudden arrhythmic death, or unclassifiable. For this analysis, SCD will be defined as definite or possible sudden arrhythmic deaths.

Covariates

Age, sex, race, study center, smoking (never, former, current), body mass index, hypertension, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, CHD, ECG-based left ventricular hypertrophy (LVH) defined by the Cornell criteria, use of anti-arrhythmic medications, use of beta-blockers, use of digoxin, and heart failure.

Statistical Analysis: SCD

Follow-up will be defined as time between the baseline exam until the date of SCD, other death, loss to follow-up, or end of follow-up, whichever occurs first. We will use Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals of aIAB for SCD.

Model 1: Age, sex, race, study center

Model 2: Model 1 + smoking, body mass index, hypertension, diabetes, CHD, LVH, use of anti-arrhythmic medications, use of beta-blockers, use of digoxin, and heart failure

Model 3: Model 2 + time-dependent AF

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.csc.unc.edu/ARIC/search.php  
___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)?

#1557 – ECG Predictors of SCD - Soliman

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  
___ A. primarily the result of an ancillary study (list number* __________)  
___x___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2004.03)

*ancillary studies are listed by number at http://www.csc.unc.edu/aric/forms/

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.csc.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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes ___x__ No.
References