ARIC Manuscript Proposal #2638

PC Reviewed: 10/13/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: ECG-Based Left Atrial Abnormality and Incident Coronary Heart Disease: The Atherosclerosis Risk in Communities Study.

b. Abbreviated Title (Length 26 characters): PTFV1 and incident CHD

2. Writing Group:

Writing group members: Ankit Maheshwari, Faye L. Norby, Wesley T. O'Neal, Selcuk Adabag, Alvaro Alonso, Elsayed Z. Soliman, Lin Y. Chen, others welcome.

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] It is often the first manifestation of significant, subclinical coronary heart disease (CHD) in affected individuals.[2–4] Thus, early detection of high-risk CHD is essential for SCD prevention.

P-wave terminal force in lead V1 (PTFV1), defined as the product of the amplitude and duration of the terminal portion of the P-wave in V1, is an ECG marker of atrial structure and function that has been associated with atrial arrhythmias including atrial fibrillation.[5] Both abnormal PTFV1 and AF have been independently associated with interstitial myocardial fibrosis and SCD.[6–9] Of note, AF has been independently linked to incident MI.[10–13] The association of AF and abnormal PTFV1 with SCD may, in part, be explained by underlying myocardial fibrosis related to CHD. We therefore hypothesize that abnormal PTFV1 is independently associated with incident CHD in the general population. Previous reports from the ARIC study and NHANES III survey have shown that deep-terminal negativity in V1, a component of the PTFV1, is associated with increased risk of fatal CHD.[14,15] However, whether this association could be extended to non-fatal CHD is unclear.

5. Main Hypothesis/Study Questions:

AIM: Evaluate the relationship between abnormal PTFV1 with CHD incidence
Hypothesis: Abnormal PTFV1 will be associated with an increased incidence of CHD, independent of other cardiovascular risk factors and incident AF.

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. We will exclude those with missing baseline covariates, missing ECG data, or with baseline AF or CHD.

Exposure
PTFV1 will be defined as the duration (ms) x the absolute value of the depth (μV) of the downward deflection (terminal portion) of the median P-wave in lead V1. Abnormal PTFV1 is defined as ≥4000 μV*ms similar to previous ARIC papers.[16]

Outcome
Incident CHD: CHD incidence is physician adjudicated as previously described.[17,18] CHD incidence is defined as definite or probable MI including silent MI detected on ECG, cardiac revascularization procedure, or definite CHD death.

Covariates

Baseline age, sex, race, study center, smoking (never, former, current), body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, LDL, HDL, triglycerides, diabetes, and ECG-based left ventricular hypertrophy (LVH) defined by the Cornell criteria, and incident AF.

Statistical Analysis

Follow-up will be defined as time between the baseline exam (ARIC visit 1) until the date of CHD diagnosis, death, loss to follow-up, or end of follow-up, whichever occurs first. For those with incident abnormal PTFV1, time between baseline and abnormal PTFV1 diagnosis will be considered as non-PTFV1 follow-up. We will use Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals of abnormal PTFV1 for CHD.

Model 1: Age, sex, race, study center

Model 2: Model 1 + smoking, body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, LDL, HDL, triclycerides, diabetes, and LVH

Model 3: Model 2 + time-dependent AF

Other analysis will include: 1) using restricted cubic spline regression to examine the risk of CHD events across the continuous spectrum of PTFV1; 2) Subgroup analysis stratified by age (median), sex and race.

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 ____ 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

   ___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
#1156 – ECG Predictors of AF and Stroke-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.cscc.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.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.

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

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