ARIC Manuscript Proposal #2596

PC Reviewed: 8/11/15 **Status: <u>A</u>** **Priority: <u>2</u>**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Advanced Interatrial Block and the Risk of Sudden Cardiac Death in the Atherosclerosis Risk in Communities Study

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

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]**

    F**irst author**: Ankit Maheshwari, MD
    Address: Cardiac Arrhythmia Center, Cardiovascular Division
            Department of Medicine
            University of Minnesota Medical School
            420 Delaware Street SE, MMC 508
            Minneapolis, MN 55455

        Phone: (630) 915-0660   Fax: (612) 624-4937
        E-mail: mahes046@umn.edu

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).
    Name: Lin Y. Chen, MD**,** MS
    Address: Cardiac Arrhythmia Center, Cardiovascular Division
            Department of Medicine
            University of Minnesota Medical School
            420 Delaware Street SE, MMC 508
            Minneapolis, MN 55455

        Phone: (612) 625-4401   Fax: (612) 624-4937
        E-mail: chenx484@umn.edu

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.[3–9]

We recently demonstrated that atrial fibrillation (AF) is independently associated with an increased risk of SCD in the general population.[10] 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 a marker of atrial structure and function. Abnormal PTFV[11] has been shown to be associated with AF and SCD in the general population.[12] Both AF and abnormal PTFV1 have been associated with interstitial ventricular myocardial fibrosis, which may represent a possible mechanism explaining the association between atrial abnormalities and SCD .[12–14] Advanced inter-atrial block (aIAB) is an ECG marker of atrial electrical abnormality defined as P wave duration >120 ms and biphasic P wave morphology is present in the inferior leads (II, III, aVF) with negative P prime deflection of any amplitude.[12] It is associated with an increased risk of atrial arrhythmias including AF.[15] We therefore hypothesize that aIAB is independently associated with an increased risk of SCD.

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

AIM : Evaluate the association of aIAB with SCD incidence
Hypothesis: aIAB will be associated with higher SCD incidence, independent of other cardiovascular risk factors, atrial fibrillation, and abnormal PTFV1.

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 covariates, missing ECG data, and those with AF at baseline.

Exposure
Advanced interatrial block (aIAB) will be defined as P wave duration >120 ms and biphasic P wave morphology is present in the inferior leads (II, III, aVF) with negative P

prime deflection of any amplitude in any of the ARIC exams. aIAB will be examined as a time-dependent variable.

Outcome
SCD: In ARIC, all CHD deaths that occurred by December 31, 2001 were reviewed 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, educational level, smoking (never, former, current), body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, use of anticoagulants, diabetes, stroke, CHD, ECG-based left ventricular hypertrophy (LVH) defined by the Cornell criteria, incident atrial fibrillation, abnormal PTFV1, and heart failure. 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 $\geq$4000 μV*ms.

Statistical Analysis

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. For those with incident aIAB, time between baseline and aIAB diagnosis will be considered as non-aIAB follow-up. 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 + educational level, smoking, body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, use of anticoagulants, diabetes, stroke, CHD, LVH, and heart failure

Model 3: Model 2 + abnormal PTFV1

Model 4: 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 __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
#2563 – aIAB and AF – O'Neal

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

1. Roger, V. L. *et al.* Heart disease and stroke statistics-2011 update: A report from the American Heart Association. *Circulation* **123,** 18–209 (2011).

2. Adabag, A. S. *et al.* Etiology of sudden death in the community: results of anatomical, metabolic, and genetic evaluation. *Am Hear. J.* **159,** 33–39 (2010).

3. Bardy, G. H. *et al.* Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* **352,** 225–337 (2005).

4. Buxton, A. E. *et al.* Limitations of Ejection Fraction for Prediction of Sudden Death Risk in Patients With Coronary Artery Disease. Lessons From the MUSTT Study. *J. Am. Coll. Cardiol.* **50,** 1150–1157 (2007).

5. Stecker, E. C. *et al.* Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: Two-year findings from the Oregon sudden unexpected death study. *J. Am. Coll. Cardiol.* **47,** 1161–1166 (2006).

6. Fishman, G. I. *et al.* Sudden cardiac death prediction and prevention: Report from a national heart, lung, and blood institute and heart rhythm society workshop. *Circulation* **122,** 2335–2348 (2010).

7. Goldberger, J. J. *et al.* American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: A scientific statement from the America. *Circulation* **118,** 1497–1518 (2008).

8. Chugh, S. S. & Reinier, K. Predicting sudden death in the general population: Another step, n terminal b-type natriuretic factor levels. *Circulation* **119,** 2863–2864 (2009).

9. Moss, A. J. MADIT-I and MADIT-II. *J. Cardiovasc. Electrophysiol.* **14,** S96–S98 (2003).

10.   Chen, L. Y. *et al.* Atrial fibrillation and the risk of sudden cardiac death: the atherosclerosis risk in communities study and cardiovascular health study. *JAMA Intern. Med.* **173,** 29–35 (2013).

11.   Tereshchenko, L. G., Shah, A. J., Li, Y. & Soliman, E. Z. Electrocardiographic Deep Terminal Negativity of the P Wave in V1 and Risk of Mortality: The National Health and Nutrition Examination Survey III. *J. Cardiovasc. Electrophysiol.* **25,** 1242–1248 (2014).

12.   Tereshchenko, L. G. *et al.* Electrocardiographic Deep Terminal Negativity of the P Wave in V1 and Risk of Sudden Cardiac Death: The Atherosclerosis Risk in Communities (ARIC) Study. *J. Am. Heart Assoc.* **3,** e001387–e001387 (2014).

13.   Tiffany Win, T. *et al.* Associations of electrocardiographic P-wave characteristics with left atrial function, and diffuse left ventricular fibrosis defined by cardiac magnetic resonance: The PRIMERI Study. *Hear. Rhythm* **12,** 155–162 (2015).

14.   Shantsila, E., Shantsila, A., Blann, A. D. & Lip, G. Y. H. Left ventricular fibrosis in atrial fibrillation. *Am. J. Cardiol.* **111,** 996–1001 (2013).

15.   Bayés de Luna, A. *et al.* Interatrial conduction block and retrograde activation of the left atrium and paroxysmal supraventricular tachyarrhythmia. *Eur. Heart J.* **9,** 1112–1118 (1988).