ARIC Manuscript Proposal # 1737

PC Reviewed: 1/11/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Atrial Fibrillation and Sudden Cardiac Death: The ARIC Study

b. Abbreviated Title (Length 26 characters): Atrial Fibrillation and Sudden Cardiac Death

2. Writing Group:

Writing group members: Lin Y. Chen, Alvaro Alonso, Faye Lopez, Elsayed Soliman, A. Selcuk Adabag, Suma Konety, Aaron R. Folsom, and others.

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

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3. Timeline:

Statistical Analysis: 3 months

Manuscript preparation: 3 months

4. Rationale:

Atrial fibrillation (AF) is the most common sustained arrhythmia afflicting more than 2 million Americans, a figure that is projected to increase to approximately 5 to 12 million by 2050.[1, 2] AF is associated with an increased risk of stroke,[3] heart failure,[4] and death.[5] Sudden cardiac death (SCD) is a major public health problem comprising more than half of all cardiovascular disease deaths in the United States.[6] Although AF is associated with a higher risk of mortality, the mechanisms of death are not fully understood. The association of AF with SCD or non-sudden CHD death (NSCD) in the general population has not been reported.

The association of AF with SCD, however, has been reported in certain patient subsets. In the Trandolapril Cardiac Evaluation (TRACE) registry, the adjusted risk ratio of AF for SCD in patients who suffered a myocardial infarction (MI) was 1.31 (95% CI: 1.07–1.60; $P<0.009$).[7] Similarly, in a hospital-based MI study, the 7-year SCD risk was higher in patients who developed AF compared with those who remained in sinus rhythm (multivariable OR: 2.7; 95% CI: 1.2–6.4; $P=0.02$).[8] In addition, AF was found to be associated with a higher risk of SCD in patients with advanced heart failure.[9] Moreover, AF is associated with channelopathies that increase risk of SCD such as short QT syndrome[10] and Brugada syndrome[11]–raising the possibility of using ECG predictors to identify patients with AF who are at higher risk of SCD. Recent data that suggest an association between J-point elevation on the ECG and the development of idiopathic ventricular fibrillation[12] further lend credence to the hypothesis that ECG parameters may be used to identify patients with AF who are at higher risk of SCD.

Previous studies have provided some insights into the determinants of SCD in patients with AF. In the Rate Control versus Electrical Cardioversion in Persistent AF (RACE) study, a history of MI was associated with a higher risk of SCD, whereas the use of β-blockers was associated with a lower risk of SCD.[13] Although these data are instructive, the determinants of SCD in patients with AF in the general population are not well understood.

ARIC–with more than 1,000 incident AF cases, 250 adjudicated SCD, and 400 NSCD cases–is uniquely suited to investigate the relationship between AF with SCD and NSCD, and the determinants of SCD in subjects with AF in the general population.

5. Main Hypothesis/Study Questions:

Aim #1: Evaluate the association between AF and risk of SCD and risk of NSCD

Hypothesis #1: In the general population, AF is associated with an increased risk of SCD, independent of other risk factors for SCD.

Hypothesis #2: In the general population, AF is more strongly associated with risk of SCD than NSCD.

Aim #2: Identify ECG predictors of SCD in subjects with AF

Hypothesis #3: In subjects with AF, J-point elevation is predictive of SCD, independent of other risk factors for 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 study the entire ARIC cohort.

Exclusion criteria for Aim #1: Indeterminate AF status and missing information on covariates.

Exclusion criteria for Aim #2: Indeterminate AF status, poor quality or missing ECG data, QRS duration ≥ 120 ms to exclude cases of bundle branch block, Wolf-Parkinson-White syndrome, and idioventricular rhythm, paced rhythm, and missing information on covariates.

Exposures measurement

AF

AF cases will be identified from:

1) Hospital discharge records (ICD-9 code 427.31 – Atrial fibrillation)
2) ECGs performed during study visits 1 – 4

ECG parameters

We will analyze 12-lead ECGs that are closest to diagnosis of AF. These parameters will be measured during sinus rhythm:

1) QRS duration
2) QTc interval
3) J-point elevation is defined as a J-point amplitude ≥1 mm (0.1mV) in any lead

Outcomes measurement

SCD

All events classified as fatal coronary heart disease (CHD) (definite MI, definite fatal CHD, or possible fatal CHD, in and out of hospital) through 2001 were reviewed and adjudicated by a committee of physicians. SCD was defined as a sudden pulseless condition from a cardiac origin in a previously stable individual. Case data were sent separately to pairs of physician adjudicators for classification. Any disagreement in classification of cause of death was resolved by separate re-coding by two senior coders. If further disagreement was present, it was resolved through discussion between the senior coders. After an extensive event review, which included abstraction of data from death certificates, informant interviews, physician questionnaires, coroner reports, and hospital discharge summaries, reviewers classified each CHD death as definite sudden arrhythmic death, possible arrhythmic death, not sudden arrhythmic death, or unclassifiable. SCD will be defined as the first 2 categories.

NSCD
All events classified as fatal myocardial infarction or definite or possible fatal CHD, which did not meet criteria for SCD.

Covariates
Age, gender, race, study center, heart rate, smoking status, body mass index, hypertension, diabetes, hypercholesterolemia, history of MI, coronary heart disease, heart failure, and use of β-blockers and anti-arrhythmics.

Statistical analysis

Aim #1
We will estimate the survival of subjects according to AF status by the Kaplan-Meier method. We will use Cox proportional hazards models with AF status as a time-dependent variable to determine whether AF occurrence is associated with the following two outcomes: SCD and NSCD, adjusting for baseline and time-dependent covariates. Model 1 will adjust for age, gender, race, and study center. Model 2 will additionally adjust for heart rate, smoking status, body mass index, hypertension, diabetes, hypercholesterolemia, history of MI, coronary heart disease, heart failure, and use of β-blockers and anti-arrhythmics. We will formally test the null hypothesis that the strength of association between AF and SCD is the same as the association between AF and NSCD.

As sensitivity analysis, we will repeat the analysis using only definite sudden arrhythmic death as definition of SCD.

Aim #2
In patients with AF, we will use Cox proportional hazards models to determine whether QRS duration, QTc interval, and J-point elevation in any lead are associated with SCD, adjusting for baseline and time-dependent covariates. Model 1 will adjust for age, gender, race, and study center. Model 2 will additionally adjust for heart rate, smoking status, body mass index, hypertension, diabetes, hypercholesterolemia, history of MI, coronary heart disease, heart failure, and use of β-blockers and anti-arrhythmics.

In addition, we will test for interactions between gender and race with ECG parameters in relation to SCD by including an interaction term in the models.

As sensitivity analysis, we will repeat the analysis using only definite sudden arrhythmic death as definition of SCD.

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 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 __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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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 tocontact lead authors of these proposals for comments on the new proposal or collaboration)?
- MS #1557: Prineas – ECG predictors of SCD
- MS #1196: Peacock – Magnesium and SCD
- MS #1601: Olson – J-point elevation and prognosis

We have included some authors above as co-authors in the current manuscript.

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
_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/

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

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