ARIC Manuscript Proposal #1156

PC Reviewed: _06/_12_/06	**Status: __A__**	**Priority: __2___**
SC Reviewed: __05/25/06__	**Status: __CA__**	**Priority: __2__**

1. a. Full Title:
"Electrocardiographic Prediction of Atrial Fibrillation and Its Impact on Understanding the Ethnic Distribution of Stroke in the ARIC Study"

b. Abbreviated Title (Length 26 characters):
AF Prediction

2. Writing Group (list individual with lead responsibility first):
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. …EZS…**confirms that all coauthors have read and approved this paper proposal]**

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3. Timeline
Start analyses: upon receipt of data from the Coordinating Center

4. Rationale: The burden of disease, particularly cerebrovascular disease, is greater among African Americans than among whites. African-Americans have a higher stroke incidence and mortality. All ischemic stroke subtype incidence rates are increased among blacks [(1)]. Being one of the commonest causes of ischemic stroke, atrial fibrillation (AF) is expected to have a higher prevalence among African Americans. However, this is not the case; AF has been mentioned by many studies to be less prevalent among African Americans. AF and its determinants failed to explain the higher incidence of stroke among African Americans in a US national study [(2)]. Difficulties in recording all cases of AF [paroxysmal AF (PAF) for example] remain an obstacle to confirm the conclusion that African Americans have a lower prevalence of AF compared to whites. Therefore, in this study we will test the ability of some ECG variables to predict incident AF in a general population. Confirming the predictive accuracy of such predictors would justify using their distribution as a clue for distribution of AF in such a population. This would enable us to take account of PAF. Additionally, if reliable AF predictors can be confirmed, the same electrocardiographic variables could be independently related to the risk of development of future stroke which is a common complication of AF.

5. Main Hypothesis/Study Questions:

Hypothesis:

- Incident atrial fibrillation/ flutter (AF/AFL) can be predicted by electrocardiographic variables derived from the 12 lead resting ECG.
- The positive electrocardiograpic predictors of AF/AFL are more prevalent among African Americans than whites.
- Electrocardiographic predictors of AF/AFL at baseline will be significantly and independently related to incident stroke for African Americans and whites.

Aim of the study:

The study will aim to:

1) Test the accuracy of some ECG variables derived from the 12-lead resting ECG to predict incident ECG diagnosed AF/AFL in African Americans and whites, men and women in the ARIC study. These variables are maximum P wave duration (P Dur), isoelectric interval (IEI) plus P wave duration, P wave dispersion (PWD), P wave variance, P wave terminal force and spatial velocity, PR interval and premature complexes detection.
2) Compare the ethnic distribution of the ECG AF/AFL gender-specific predictors
3) Test the relation between the ethnic distribution of AF/AFL predictors at baseline and the ethnic distribution of incident stroke in African Americans and whites, men and women in the ARIC study

Background

The AF predictors which will be used in the study are:

1. Maximum P wave duration (P Dur)

An abnormal prolongation of P wave duration on the surface ECG reflects the presence of intra-atrial conduction defects. [3] A slowed conduction is a prerequisite for development of a reentrant arrhythmia as the shortening of refractory period makes the atrial tissue variably sensitive to atrial premature depolarization. The studies of Dilaveris et.al.[3], Aytemir et. al. .[4] and Andrikopoulos et.al.[5] showed that maximum P wave duration has sensitivity, specificity and positive predictive accuracy to predict AF as high as (88%, 83%, 88%), (75%, 72%, 75%) and (84%, 79%89%) respectively. Dilaveris et.al., and Andrikopoulos et.al. used a cut point of 110 ms P duration and Aytemir et. al. used 106 ms P duration.

2. Isoelectric interval (IEI)

The isoelectric interval (IEI) is defined as the difference between total P wave duration and maximum P wave duration. A higher value is present in patients developing AF than in control subjects. The actual meaning of this indicator is not well established, yet. Buxton and Josephson [6] proposed some possible explanations. The most likely of all seems to be that a prolongation in the isoelectric interval is the result of the asynchronous atrial activation due to anatomic and electrophysiologic alterations predisposing to AF. However a prolongation of the IEI is not a good predictor for the arrhythmia, unless used in combination with P wave duration. Buxton and Josephson [6] reported that total P duration of 100 ms + IEI$\geq$ 10ms has a sensitivity of 66%, specificity of 70%, positive predictive accuracy of 48% and negative predictive accuracy of 83%

3. P wave dispersion (PWD)

Dilaveris *et al.* presented a novel predictor for AF after coronary artery by bass graft surgery (CABG) that they named P wave dispersion (PWD). [3] It is defined as the difference between the maximum and the minimum P wave duration detected in a 12-lead standard ECG. A lead-variable P wave duration is an indicator of the site-dependent inhomogeneous variability of the atrial conduction delay that is considered as one of the predisposing conditions to AF [4]. This condition can be easily identified through observation of differently oriented ECG leads recordings. This means that P wave dispersion can be used as a marker of this alteration, thus indicating patients at risk for developing AF. The studies of Dilaveris et.al.[3] and Aytemir et. al. .[4] showed that P wave dispersion at cut point of 40 ms and 36 ms has sensitivity, specificity and positive predictive accuracy to predict AF as high as (83%, 77%), (85%, 82%) and (89%, 85%) respectively. When P max is added to the equation (P max+ PWD) the sensitivity, specificity and positive predictive accuracy to predict AF became as high as (75%, 70%), (92%, 92%) and (95%, 92%) respectively.

4. P wave variance

It is defined as the square of the standard deviation of P waves durations and calculated as:

$$P_{var} = \frac{n\Sigma x_i^2 - (\Sigma x_i)^2}{n^2}$$

Where *n* is the number of P waves and *xi* represents the P wave duration at the instant *i*. Like P dispersion it is an indicator of the conduction variability but it is less dependent on P wave morphology and more reproducible [5]

5. P terminal force and spatial velocity

P terminal force is usually used as an indicator of left atrial abnormality [7]. As atrial enlargement is often a concomitant AF disease, Stafford *et al*. tested this parameter as an ECG marker of atrial alteration predisposing to AF [8]. It is defined as the duration (in seconds) of the terminal part (negative) of the P wave in lead V1 multiplied by its depth in millimeters. If the P wave terminal part is positive, then the interval extending from the first notch to the wave end must be considered. The spatial velocity is the rate of change of the P wave voltage with respect to time.

6. PR interval

Passman *et al.* [9] showed that a prolonged PR interval measured from lead V1 is a risk factor for post-CABG AF . More information about conduction delay can be obtained through a V1 lead recording because of its spatial orientation: its terminal portion reflects the posterior atrial potential that cannot be recorded through a limb lead.

7. Premature complexes detection

Kolb *et al*. analyzed 297 spontaneous episodes of AF in 33 patients [10]. They found that atrial premature complexes (APC) initiated 93% of them. This cause-effect mechanism is even more evident when considering atrial premature complexes with an aberrant P wave morphology [11]. Vikman *et al.* also found that the number of ectopic beats seems to increase prior to the arrhythmia onset [12]. Schreier *et al*., hypothesized that a P wave showing an inverse signal morphology when compared to the neighboring P waves might be a potential trigger for the onset of paroxysmal AF [13]. Patients showing a higher number of atrial ectopic beats should thus be at higher risk for AF.

References

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6. Data (variables, time window, source, inclusions/exclusions):

- **ECG Variables:**

A new ARIC ECG database file will be prepared for the study excluding:

- ECGs that possibly could affect the P wave or PR interval measurements. This includes:
  - Advanced degree heart block
  - Wolf Parkinson White Syndrome (WPW)
  - Artificial pacemaker
  - Ventricular fibrillation, ventricular asystole and persistent ventricular tachycardia (if any)

- Poor quality ECG i.e. quality control grade 5 ECGs

The ECG file will include ECGs at the baseline visit, each scheduled ARIC visit and all stroke hospitalizations

ECG variables needed to fulfill the aim of the study will be:

- AF/ Atrial Flutter (AFL)
- P wave duration
- Isoelectric interval + P wave duration
- P wave dispersion
- P wave dispersion + P wave duration
- P wave variance
- P terminal force and spatial velocity

- PR interval
- Premature complexes detection

It is expected to have an ECG file that contains 15586 baseline ECGs

Non-ECG variables:

Non-ECG variables include demographic data, outcome measures, medical history and haemostatic measure. These variables are summarized in the table below (tables 1)

Table(1): Non-ECG variables quoted from the list of variables of ARIC population

Demos/descriptives		
V1AGE01	AGE AT VISIT 1	
V1DATE01	VISIT 1 DATE	
RACEGRP	RACE	FORMAT is $RACE
BMI01	BODY MASS INDEX IN KG/(M*M)	
BIRTHDAT	DATE OF BIRTH OF SUBJECT	
GENDER	SEX	
OUTCOME		
FATALSTR	Fatal Stroke (Classified by ARIC)	FORMAT is YN
DTH18	Underlying cause of death from DTHA18	ICD9/10 for all deaths
IN02DP	Definite/Probable Incident Stroke	FORMAT is YN
IN02DPP	Definite/Probable/Possible Incident Stroke	FORMAT is YN
IN02ISC	Def/Prob Ischemic Incident Stroke	FORMAT is YN
IN02HEM	Def/Prob Brain Hemorrhagic Incident Stroke	FORMAT is YN
IN02CHM	Def/Prob Brain/SAH Hemorrhagic Incident Stroke	FORMAT is YN
ED02DP	End Date for IN02DP	For calculation of "time-to-event"
ED02DPP	End Date for IN02DPP	For calculation of "time-to-event"
ED02ISC	End Date for IN02ISC	For calculation of "time-to-event"
ED02HEM	End Date for IN02HEM	For calculation of "time-to-event"
ED02CHM	End Date for IN02CHM	For calculation of "time-to-event"
DEADYY	Dead by end of year 2002	FORMAT is YN
STROKE01	Stroke	FORMAT is $STR (Patient has had a stroke at visit 1)
DEATHCODE	Underlying Cause of death code	ICD9/10 for sudden deaths
DTHDATE2	Death Date for a Person	
PRVSTR21	Prevalent Stroke at V2	FORMAT is YN
Medical History		
FHXA14	DID 1st SIBLING EVER HAVE A STROKE? at V2 Q14	FORMAT is $YNFMT
FHXA23	DID 2nd SIBLING EVER HAVE A STROKE? at V2 Q23	FORMAT is $YNFMT
FHXA32	DID 3rd SIBLING EVER HAVE A STROKE? at V2 Q32	FORMAT is $YNFMT
FHXA41	DID 4th SIBLING EVER HAVE A STROKE? at V2 Q41	FORMAT is $YNFMT
FHXA50	DID 5th SIBLING EVER HAVE A STROKE? at V2 Q50	FORMAT is $YNFMT
FAMHXSTR	Family history of stroke	FORMAT is $FAM
DIABTS02	DIABETES (cut point of 140)	FORMAT is YN
DIABTS03	DIABETES (cut point of 126)	FORMAT is YN
Remaining variables		
TIABFLAG	FLAG INDICATING PRESENCE OF TIA	

Data analysis:

First, frequency distributions of all ECG and Non-ECG variables will be inspected to rule out anomalies and outliers possibly due to measurement artifacts.

The main ECG file will be divided into tow sub-files one includes the ECG data of patients with AF/AFL at the baseline (ECG file 1) and the other (ECG file 2) contains the ECG data of patients without AF at their baseline

The incidence of the ECG diagnosed AF/AFL according to sex, age and development of stroke will be compared in African Americans versus whites using Chi square test

To test the value of each of the ECG variables as a predictor for development of AF/AFL, ischemic stroke and stroke mortality, Cox regression analysis and Kaplan-Meier survival curves will be used. This will be done separately for each ECG variable and then in combination with other variables using multiple regression analysis. ECGs collected during stroke hospitalizations as well as these collected during the scheduled visits will be used in the data analysis.

Each ECG variable will first be tested as a continuous variable then as a dichotomized variable at a certain cut point that will be identified according to the future preliminary analysis. The rationale for using dichotomized in addition to the continuous exposure is that the results from this approach can be easily translated into useful clinical information that could help other future diagnostic or prognostic studies besides its use in daily clinical practices.

All risk models will first be adjusted for age alone and subsequently for age and other demographic and clinical variables mentioned before under non-ECG variables

The proportional hazards assumption of the Cox model will be checked graphically for each of the candidate variables. All analyses will be performed with the SAS system for Windows, version 9.0.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?

There are none

11. 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.