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Modified further 6/8/6

PC Reviewed: _05/_23_/06	**Status: __A__**	**Priority: __2___**
SC Reviewed: __05/25/06__	**Status: __A__**	**Priority: __2__**

1. a. Full Title:
"Comparison of The Prognostic Significance of The Frontal Plane QRS/T Axis Angle, Spatial QRS/T Angle, and ST-T Abnormalities For Prediction Of Coronary Heart Disease Outcome and Total Mortality in the Atherosclerosis Risk In Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters):
QRS/T angle

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. …ZMZ…**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 centre
Submission for publication: July 2007

4. **Rationale**: Being available, noninvasive, and inexpensive the routine resting electrocardiogram (ECG) has become the most widely used cardiovascular (CV) test. Not only is it useful as a diagnostic tool when dynamic changes are expected as in patients with chest pain, but also static findings on the routine ECG are a simple way of stratifying patients' risk for CV mortality [1]. One of the recent interesting ECG derived predictors is the spatial QRS/T angle. Abnormal angles had a hazard ratio of 5.6 for sudden cardiac death (SCD) [2]. None of the classic CV and ECG predictors provided larger hazard ratios. This has been tested in a general population [2], an elderly population [3] and a clinical population [4]. Limited by its sophisticated computer based measurement, spatial QRS/T axis can not be used in day to day clinical practice. Additionally, this measure is not familiar to most clinicians and is not routinely available from computerized ECG analysis software currently in use, which potentially limits its applicability [5]. In this study we will test the prognostic significance of the angle between the frontal plane electrical axes of QRS and T waves (QRS/T electrical axis angle) in prediction of incidence of and mortality from CHD as well as total mortality in comparison with spatial QRS/T axis angle. The QRS/T frontal plane electrical axis angle is readily available from the 12 lead ECG and is understood by clinicians. Most outputs from recent electrocardiographs routinely quote the QRS and T axes as basic measurements. Hence, frontal plane QRS/T electrical axis angle could be a useful clinical tool to stratify the risk of CHD morbidity and mortality in the general population. Although there are some recent studies on the prognostic significance of the spatial QRS/T axis and/or T wave electrical axis [2], [3] [4] [6] [7] for prediction of morbidity and mortality from CHD in different populations, there are no published data about the prognostic significance of QRS/T electrical axis angle in any subset of the population. The prognostic value of the QRS/T electrical axis angle to predict morbidity and mortality from cardiovascular disease is plausible. In normal individuals it is expected that the electrical axis of the T wave goes with the electrical axis of the QRS [8]. Divergence of both axes is expected when there is a change in the T wave without a corresponding change in the QRS, which is the case in myocardial ischemia. At abnormal cut points both frontal plane QRS/T electrical axis angle and spatial QRS/T angle are associated with concomitant abnormal ST/T wave abnormalities (which we have observed in another data set in preliminary analysis at EPICARE). Therefore, the advantage of the QRS/T angle- in both frontal and spatial planes- over observation of the usual ST-T changes for CHD prognosis will also be tested.

References:

1- Engel J, Beckerman J, Froelicher V, Yamazaki T, et. al., Electrocardiographic arrhythmia risk testing. Current Problems in Cardiology. July 2004: 365

2- Kardys I, Kors JA, van der Meer IM, Hofman A, van der Kuip DA, Witteman JC. Spatial QRS-T angle predicts cardiac death in a general population. Eur Heart J 2003; 24:1357-64.

3- Kors JA, Kardys I, van der Meer IM, Herpen JV, et al. Spatial QRS-T Angle as a Risk Indicator of Cardiac Death in an Elderly Population. Journal of Electrocardiology Vol. 36 Supplement 2003
4- Yamazaki T, Froelicher VF, Myers J, Chun S, Wang P. Spatial QRS-T angle predicts cardiac death in a clinical population. Heart Rhythm, Vol 2, No 1, January 2005
5- Okin PM. Electrocardiography in women: taking the initiative. Circulation 2006;113(4):464-6
6- Rautaharju PM , Kooperberg C, Larson JC, La Croix A. Electrocardiographic predictors of incident congestive heart failure and all-cause mortality in postmenopausal women: the Women's Health Initiative. Circulation 2006;113(4):481-6
7- Algiakrishnan K, Beitel J, Graham M, et. al., Relation of T-Axis abnormalities to coronary artery disease and survival after cardiac catheterization. Am J Cardiol 2005:96:639-642
8- Clinical Electrocardiography. Goldberger AL. Six edition, 1999 Mosby, Inc.

5. Main Hypothesis/Study Questions:

This study aims to:

(1) Test the prognostic significance of the baseline measurement of QRS/T frontal plane electrical axis angle as a potential clinical predictor for the incidence of combined non-fatal CHD and fatal CHD events and total mortality in the population of the Atherosclerosis Risk in Communities Study (ARIC)

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(2) Compare the prognostic value of the QRS/T frontal plane electrical axis angle with the spatial QRS/T angle for prediction of combined non-fatal CHD and fatal CHD events and total mortality in the population of the Atherosclerosis Risk in Communities Study (ARIC)

(3) Compare the prognostic value of the QRS/T frontal plane axis angle and ST-T abnormalities for prediction of combined non-fatal CHD and fatal CHD events and total mortality in the population of the Atherosclerosis Risk in Communities Study (ARIC)

(4) Compare the prognostic value of the spatial QRS/T axis and ST-T abnormalities for prediction of the incidence of combined non-fatal CHD and fatal CHD events and total mortality in the population of the Atherosclerosis Risk in Communities Study (ARIC)

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

- **ECG Variables:**

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

- ECGs with Minnesota codes that suppress Minnesota codes 4 and/or 5. Specifically, ECGs with:
  - Complete heart block
  - Wolf Parkinson White Syndrome (WPW)
  - Artificial pacemaker
  - Left bundle branch block- persistent and intermittent

        - Complete right bundle branch block (incomplete right bundle branch block)
        - Intraventricular conduction delay, QRS $\geq$ 120ms
        - Ventricular fibrillation, ventricular asystole and persistent ventricular tachycardia (if any)
        - Ectopic atrial rhythm with heart rate over 140 beat per minute

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

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

- QRS frontal plane electrical axis
- T wave frontal plane electrical axis
- QRS/T frontal plane electrical axis
- Spatial QRS/T angle
- ST segment (Minnesota code 4 and Novacode)
- T wave (Minnesota code 5 and Novacode)
- ECG-MI data (Minnesota code 1 and Novacode)

It is expected to have an ECG file that contains 14472 baseline ECGs of ARIC subjects with ECG data available and without any ECG exclusion.

Non-ECG variables:

Non-ECG variables include demographic data, outcome measures, medical history and haemostatic measure. These variables are summarized in table (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 measures		
SUDDEN_DEATH	Definite/Possible/No for sudden death	FORMAT is SUDDEN
CENSDAT5	Censoring date by 2002 for all events	
DEATHCODE	Underlying Cause of death code	ICD9/10 for sudden deaths
DTH18	Underlying cause of death from DTHA18	ICD9/10 for all deaths
DTHDATE2	Death Date for a Person	
FATCHD3	Fatal CHD (Classified by ARIC)	FORMAT is YN
IN_BY02	Incident MI/CHD by end of 2002	FORMAT is YN
INC_BY02P	Incident MI/CHD/Procedure by end of 2002	FORMAT is YN
IN_02S	Incident MI/CHD/ECG MI by end of 2002	FORMAT is YN
IN_02SP	Incident MI/CHD/ECG MI/Procedure by end of 2002	FORMAT is YN
CARDPROC	Incident cardiac procedure by end of year 2002	FORMAT is YN
SMI_BY02	Incident ECG MI by end of year 2002	FORMAT is YN
MI02	Incident MI be end of year 2002	FORMAT is YN
FATCHD02	Fatal CHD by end of year 2002	FORMAT is YN
SMIDATE	End date for SMI_BY02	For calculation of "time-to-event"
DATEMI	End date for MI02	For calculation of "time-to-event"
DEADYY	Dead by end of year 2002	FORMAT is YN
MI3	Definite/probable MI	FORMAT is YN
POSDIA3	MI or FATCHD	FORMAT is YN (def/prob MI or def fatal CHD/MI)
PREVMI05	prevalent MI (composite ECG OR MED HIST)	FORMAT is YN
PRVCHD05	PREVALENT CORONARY HEART DISEASE	FORMAT is YN
Medical History		
HXOFMI02	HISTORY OF MYOCARDIAL INFARCTION	FORMAT is YN
DIABTS02	DIABETES (cut point of 140)	FORMAT is YN
DIABTS03	DIABETES (cut point of 126)	FORMAT is YN
MDDXMI02	MD DIAGNOSED MYOCARDIAL INFARCTION	FORMAT is YN
Lipids/haemostatic		
HYPERT05	HYPERTENSION, DEFINITION 5	

Data analysis:

The study endpoints will be combined fatal and nonfatal CHD, CHD death and total mortality.

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

To test the value of QRS/T electrical axis angle as a predictor of CHD morbidity and mortality and total mortality, Cox regression analysis and Kaplan-Meier survival curves will be used. QRS/T electrical axis angle 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 in patients with CHD besides its use in daily clinical practices.

For the purpose of comparison, QRS/T spatial angle and ST-T abnormalities will undergo the same statistical tests. Also for the same purpose of comparison, correlation analysis will be done between QRS/T axis angle, spatial QRS/T electrical angle and ST-T abnormalities detected by Minnesota coding system and Novacode

There is a possible interaction between the baseline CHD status and the ECG exposure variables. To account for such potential differences between the baseline CVD and CVD-free groups on the effect of the ECG markers under question on the outcomes, a series of single ECG variable proportional hazards models will be evaluated. Each model will be stratified by baseline CVD status and will include the ECG variable of interest (as an explanatory variable), an interaction term between the ECG variable and baseline CVD status, and any adjustment variables.

All risk models will be first 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)?

Combined ARIC/CHS ancillary study

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.