ARIC Manuscript Proposal #1919

PC Reviewed: 3/20/2012 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:

Prognostic Significance of Bundle Branch Blocks as Independent Predictors of Incident Heart Failure in the Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters):
Bundle Blocks & Heart failure

2. Writing Group:
Writing group members:

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

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3. Timeline:

Start analyses: upon receipt of data from the coordinating centre
Submission for publication: December 2012

4. Rationale:

Cardiovascular disease continues to be a major cause of death and disability worldwide, with a rising epidemic of heart Failure (HF) in aging populations[1] Most HF is a consequence of ischemic, or hypertensive. Abnormalities of the ST-T waves, and widening of the QRS/T angle in the resting electrocardiogram (ECG) have been associated with incident heart failure, coronary heart disease (CHD), and all-cause mortality in the general population.[2-7] Furthermore, bundle branch blocks (BBBs), both left (LBBB) and right (RBBB), have been shown to be predictive of all-cause mortality and incident HF in selected populations[8-17]

However, the presence of complete BBB is thought to limit the utility of the ECG in evaluating myocardial ischemia, where it is more difficult to categorize the accompanying appearance of abnormal depolarization and repolarization of the heart. LBBB, in particular, is characterized by repolarization changes in which the ST segments are discordant to the major direction of the QRS complex. Although the prognostic significance of these repolarization abnormalities associated with BBB have been shown for mortality and overall CHD in postmenopausal women[9], these abnormalities have not been specifically tested for measuring ischemia as a predictor of CHF in men or women. Also it is not entirely clear whether different patterns of BBB (LBBB, RBBB, intraventricular conduction defects (IVCD)) or prevalent versus incident BBB have different predictive value or not.

The aim of this study is to evaluate the prognostic significance of prevalent and incident BBB (LBBB, RBBB and IVCD, separately) in predicting incident HF, and to evaluate whether the prognostic value of BBB for HF will be enhanced by combining with ischemia-related ECG parameters including QRS/T angle (spatial or frontal planes), discordance of repolarization by various measures such as maximal ST and T deviation and the net QRS integral in representative leads of various lead groups, and rate-adjusted QT interval, separately.

5. Main Hypothesis/Study Questions:

<u>This study aims to</u>:

(1) Estimate the prognostic significance of baseline '*prevalent*' LBBB, RBBB, and IVCD, separately, for the prediction of incident heart failure in the ARIC study.

(2) Estimate the prognostic significance of '*incident'* LBBB, RBBB, and IVCD, separately, for the prediction of incident heart failure in the ARIC study.

(3) Examine the added predictive value of combining BBB (LBBB, RBBB, and IVCD, separately) with repolarization abnormalities (spatial and frontal QRS/T angle maximal ST and T deviation and the net QRS integral in representative leads of various lead groups, and rate-adjusted QT interval) for prediction of heart failure in the ARIC study.

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 methodological limitations or challenges if present).

Sample Size

All ARIC participants with good quality baseline ECG data as well as information on all relevant risk factors and outcome events of CHF during ARIC follow-up will be eligible for inclusion in this analysis. Participants with artificial pacemaker, or Wolf Parkinson White Syndrome will be excluded. From the total of 15,571 ARIC participants at baseline we expected to have approximately 450 ECGs with BBB, and 2000 ECGs with QRS duration ≥ 120ms through 4 visits. There are approximately 1800 incident heart failures in the total cohort during a maximum of 17 years follow-up through 2006.

The Variables:

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

Complete Minnesota codes[18-19] for all ECGs at baseline and follow up visits, which will include specifically,

- Complete left bundle branch block (MC-7.1)
- Complete right bundle branch block (MC-7.2)
- Combination of RBBB and left anterior fascicular block (MC-7.8)
- Intraventricular conduction defect, QRS ≥ 120ms (MC-7.4).
- ECG- Myocardical infarction/Ischemia -- MC 1, MC 4, MC 5, MC 92 --Q/QS wave, ST segment, T wave amplitude.
- Frontal QRS axis and T axis, and QRS/T angles (spatial and frontal)
- Continuos measurements of the duration and amplitude of Q-R-S-T wave by lead.
- Presence of arrhythmias and ectopic beat including atrial and ventricular ectopic beats and atrial fibrillation.

Non-ECG variables:

Non-ECG variables include demographic and clinic data, and outcome measures, which are summarized in below:

(1) The key demographic and clinical variables -- age, race, gender, body mass index, education, smoking status, alcohol use, hypertension, diabetes mellitus, cancer, emphysema, previous stroke, history of cardiovascular disease, family history of coronary heart disease, HDL cholesterol, LDL cholesterol, total triglycerides, total cholesterol, systolic blood pressure, diastolic blood pressure, hematocrit, white blood cell, baseline fasting blood glucose, insulin, creatinine, fibrinogen, and uric acid.

(2) The outcome includes updated incident heart failure confirmed by the endpoints committee (update to the end of 2006).

INCHF06	Incident HF (from discharge codes)

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.

Time dependent Cox regression analysis will be used to examine the risk of incident heart failure and the association with each pattern of BBB (LBBB, RBBB, and IVCD) as predictors for incident heart failure.

Models will be initially adjusted for demographic (age, sex, race), then further adjusted for clinical characteristics (which are the variables mentioned as non-ECG variables above). Similar analysis will be conducted for QRS duration, QRS/T angle (spatial and frontal), amplitude of Q-R-S by leads, magnitude of ST segment elevation or depression in leads with predominantly positive or negative QRS complexes (discordant or concordant of QRS complex and ST segment), magnitude of T wave change in leads with predominantly positive or negative QRS complexes (discordant or concordant of QRS complex and T wave), separately and combined with BBB patterns. Interaction by sex, race, and history of CVD will be examined and models will be stratified accordingly.

The proportional hazards assumption of the Cox regression model will be checked graphically for each of the candidate variables. All analyses will be performed with the SAS software, version 9.2.

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

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)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes _X_ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)

*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.

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