1.a. Full Title: Relationship between electrocardiographic QRS duration, cardiac structure and function, and incident heart failure in African-Americans in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): QRS, Echo, & Heart Failure

2. Writing Group:

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

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3. Timeline: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months of data becoming available.
4. **Rationale:**

Prolonged QRS duration may be a marker of adverse cardiac remodeling and carries prognostic significance among patients with heart failure (HF) and reduced ejection fraction. In this group, QRS width identifies patients who may benefit from cardiac resynchronization therapy (CRT), which has been demonstrated to reduce cardiovascular morbidity and mortality and promote reverse remodeling. These data suggest that QRS duration is not only a marker of risk in HF patients, but is also an important target for therapeutic intervention.

QRS duration may also be a marker of cardiovascular risk in those without HF. Left bundle branch block has been associated with increased risk for the development of HF in men. The Framingham Heart Study (FHS) extended these results to both genders by demonstrating that complete bundle branch block (QRS ≥ 120 msec) portended an increased risk for incident HF in both men and women. Additionally, the Losartan Intervention For Endpoint (LIFE) reduction Trial of hypertensive participants with left ventricular hypertrophy, demonstrated that persistence or development of QRS ≥ 110 msec was associated with twice the risk of incident HF as compared to those with QRS < 110 msec and left bundle branch block increased the risk of HF (hazard ratio 1.7 [95%CI 1.15-2.56]). However, the FHS included predominantly older (mean age 70 yrs) Caucasian participants while the LIFE trial included a high risk population with hypertension and left ventricular hypertrophy. Electrocardiographic predictors of incident HF were assessed in the Atherosclerosis Risk in Communities study in participants free from prevalent HF and coronary artery disease. QRS duration was not found to be a predictor of incident HF, however those with QRS duration > 120msec were excluded. Furthermore, the relationship between QRS duration and incident HF was not assessed according to race.

In patients with HF and reduced ejection fraction, increased QRS width is a marker of dyssynchrony and cardiac remodeling. However, there have been few analyses of cardiac structure and function in relation to QRS duration among patients without HF. The FHS found that increasing QRS duration was associated with left ventricular mass and dimensions and inversely associated with systolic function. In a cardiac MRI sub study of patients enrolled in the ONTARGET or TRANSCEND parallel trials, LV mass and volumes increased in relation to QRS width. However, these studies included predominantly non-black or African-American populations and in the case of ONTARGET/TRANSCEND, all patients were at high cardiovascular risk based on the presence of vascular disease and/or diabetes mellitus with end organ dysfunction.

The risk for heart failure according to QRS duration, in particular among those with QRS duration ≥ 120msec and among a middle aged community dwelling cohort of African-Americans, is largely unknown. Furthermore, the associations between cardiac structure, function, and QRS duration in African-Americans are not well understood. The Atherosclerosis Risk in Communities study is well-suited to describe the relationships between QRS duration and cardiac structure and function, as well as QRS duration and incident HF in middle aged African-Americans. The analyses proposed here will build upon prior and ongoing work in ARIC by specifically examining the relationship between QRS duration and incident HF among African Americans. Additionally, these analyses will also address the associations between QRS duration and cardiac structure and function in African Americans by utilizing the echocardiograms performed at Jackson during visit 3.

5. **Main Hypothesis/Study Questions:**
Main Objectives:
1) Describe the relationship between electrocardiographic QRS duration and cardiac structure and function in African Americans
2) Describe the relationship between electrocardiographic QRS duration and incident heart failure in African Americans

Aims:
1) Describe clinical characteristics according to QRS duration and type of ventricular conduction delay
2) Describe the cross sectional associations between cardiac structure and function and QRS duration in African-Americans
3) Describe the incidence rates of heart failure according to QRS duration and type of ventricular conduction delay in African Americans
4) Describe the risk of incident heart failure according to QRS duration and type of ventricular conduction delay in African Americans
5) Describe the incidence of HF according to QRS duration in African-Americans with preserved left ventricular ejection fraction (≥50%) or reduced (<50%) LVEF.

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).

This will be a longitudinal study of ARIC cohort participants beginning at visit 3 because this is the visit when echocardiography was performed in the Jackson participants.

Study population
To be included in the analysis the participant must have undergone electrocardiography with available measurements for QRS duration and ventricular conduction delay. Exclusion criteria include:
- Prevalent or missing HF status at visit 3
- Use of antiarrhythmic drugs at visit 3
- Missing covariate data (BMI, diabetes, hypertension, prevalent CHD, prior stroke, smoking status, alcohol status, systolic BP, diastolic BP, glucose, total cholesterol)
- Wolf Parkinson White/preexcitation on ECG
- Paced rhythm

Prevalent HF at visit 3 will be defined as those who had prevalent HF at visit 1 (by Gothenburg Criteria or use of HF medications) or those with incident HF between visits 1 and 3 according to hospitalization discharge summaries with ICD-9 codes 428.xx. Anti-arrhythmic medication use will be identified with the Medi-Span Therapeutic Classification system (codes = 350000, 350500, 351000, 352000, 353000, 354000, and 355000). Covariates will be defined according to standard ARIC definitions. Wolf Parkinson White and Paced rhythm will be identified using the Minnesota Coding System for ECG, using codes 6-4-1 or 6-4-2 and 6-8, respectively.

Exposure and covariates
Participants will be categorized according to QRS duration (<100, 100-119, and ≥120 msec). Those with QRS ≥120 msec will be further categorized according to the type of
ventricular conduction delay, i.e. Left bundle branch block (LBBB), right bundle branch block (RBBB), RBBB with left anterior fascicular block (LAFB), or intraventricular conduction delay (IVCD) using Minnesota codes (7-1, 7-1-1, 7-1-2 for LBBB, 7-2, 7-2-1, 7-2-2 for RBBB, 7-8 for RBBB+LAFB, and 7-4 for IVCD).

Clinical characteristics, echocardiographic cardiac structure and function, and outcomes (incident HF) will be compared between categories of QRS duration, based upon data variables collected at visit 3. In particular, clinical variables to be evaluated include: age, sex, hypertension, use of antihypertensive medications, diabetes mellitus, coronary artery disease, interim myocardial infarction, lipid levels, smoking status, body mass index, and blood pressure. Electrocardiographic parameters, in addition to QRS duration, will include left ventricular hypertrophy, QRS/T angle, as well as ST/T changes. Echocardiographic variables to be evaluated include: left atrial size, left ventricular (LV) size, aortic root dimension, LV fractional shortening and ejection fraction, valvular disease, mitral annular calcification, aortic valve fibrosis, LV wall thickness, LV mass, LV geometry, LV stroke volume and cardiac output, Doppler mitral inflow E and A wave peak velocities, and E/A ratio.

Outcome
The primary outcome of interest will be incident heart failure, defined as the first hospitalization with an ICD-9 code of 428.xx on the discharge summary or death with heart failure listed as the primary cause on the death certificate. The follow up period will be defined as the time elapsed from the visit 3 date to the date of incident HF, date of last contact for those lost to follow-up, or December 31, 2009.

For the relationship between QRS duration and cardiac structure and function, the primary dependent variables of interest will be LV mass, LV geometry, and LV ejection fraction.

Statistical analyses:
Categorical variables will be compared via χ2 or Fischer exact test, while continuous data will be compared between groups via a non parametric trend test. P values < 0.05 will be considered significant. Incidence rates for heart failure will be calculated as number of events divided by person time at risk and will be stratified by category of QRS duration or type of ventricular conduction delay. Time to event analysis will be performed according to the Kaplan Meier method with the log-rank test used to assess for differences. Univariate and multivariate hazard ratios for incident heart failure will be estimated using Cox proportional hazards regression.

Univariable and multivariable linear and logistic regression analysis will be used to assess associations between QRS duration as a continuous and categorical variables and echocardiographic characteristics. Adjustments for differences in clinical characteristics (based upon P <0.05 and/or clinically important covariates) will be performed. Effect modification by gender and LVEF will also be tested. Sensitivity analyses excluding those participants with prevalent coronary artery disease at baseline will also be performed. Additionally, we will evaluate the relationship between repolarization abnormalities e.g. QRS/T angle and ST/T changes, and their relationship to cardiac structure and function as well as incident heart failure among those with QRS < 120 msec.

Limitations
QRS duration will only be assessed at visit 3 and thus the association between QRS duration and incident heart failure would not take into account the QRS duration at the time of incident HF event. Incident HF will be defined from ICD-9 codes from hospitalization discharge summaries that were not further adjudicated. However, this definition has been previously validated and utilized in ARIC. Echocardiographic data is based upon M-mode, 2 dimensional, and blood flow Doppler measurements. Thus, ejection fraction and grading of diastolic function will not be assessed using current American Society of Echocardiography recommendations. Nevertheless, Teichholz’ method for LVEF has previously been validated and transmitral E and A wave velocities and the E/A ratio to describe diastolic function have been previously published from ARIC.

7.a. Will the data be used for non-CVD analysis in this manuscript? ___ Yes ___ 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 ___ 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)?

1) Zhu-ming Zhang, Pentti Rautaharju, Ronald J Prineas, Laura Loehr, Wayne Rosamon, Elsayed Z Soliman. Prognostic Significance of Bundle Branch Blocks as Independent Predictors of Incident Heart Failure in the Atherosclerosis Risk in Communities Study (ARIC). MS Proposal #1919.

- In this analysis, the risk of incident heart failure according to prevalent BBB at visit 1 as well as the risk of incident heart failure following the development of BBB during ARIC visits 2-4 will be assessed. Similar analysis for QRS duration will be performed. The analyses proposed here differs in that we will specifically evaluate African Americans from the
Jackson cohort at visit 3 when data regarding cardiac structure and function is also available.

   • In this analysis, QRS duration was not identified as predictor of incident heart failure. However, it should be noted that those with QRS ≥ 120 msec were excluded from the analysis. Furthermore, Cornell product, which does take into account QRS duration, was found to be a significant predictor of incident heart failure on univariate analysis, but was not included in multivariable models. Finally, this analysis was performed using ECG data from visit 1, rather than visit 3 as proposed here.

   • In this proposed analysis, associations between ECG and echocardiographic features were to be assessed. However, longitudinal relationship to heart failure outcomes was not specified.

   • This proposal seeks to explore whether echo variables of LV structure and function are predictors of incident HF and CV events. For the analysis proposed, we intend to look at the cross sectional relationships between cardiac structure and function.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes   ___ 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.cscce.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.cscce.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.

References:

4. Linde C, Abraham WT, Gold MR, Daubert C. Cardiac resynchronization therapy in asymptomatic or mildly symptomatic heart failure patients in relation to etiology: Results from the reverse (resynchronization reverses remodeling in systolic left ventricular dysfunction) study. J Am Coll Cardiol. 2010;56:1826-1831


