1. **Full Title:** The Predictive Value of CHF in HFrEF and HFpEF in African Americans: the ARIC Study

   **Abbreviated Title:** The prediction of CHF in African Americans

2. **Writing Group:**

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3. Timeline:

Analysis ........................................... July-August, 2014
Manuscript Writing ......................... September-October 2014
Initial Draft ....................................... October, 2014
Editing- Final Draft .............................. November 2014
Draft Submitted to P and P Committee ... December, 2014
Submission to Journal for Publication ... January 2015

4. Rationale:

African Americans (AA) are at greater risk of congestive heart failure (CHF) relative to non-Hispanic whites in the United States. AA in the south-eastern US are at particularly high risk of CHF, with Mississippi (home of the Jackson Heart Study, JHS) being one of the most afflicted states. Early identification of AA who are at risk and formulating CHF prevention strategies will contribute substantially to lowering the burden of disease in this group and address the disparities in morbidity and mortality in this vulnerable segment of the US population.

Fortunately, studies have highlighted that the precursors of CHF risk are similar across ethnicities: the higher CHF rates in AA is largely attributable to a higher frequency of elevated risk factors in this group, thereby underscoring the opportunity for prevention. It is noteworthy that AA have: a greater prevalence of hypertension (HTN, occurring at earlier ages and marked by higher average BP), obesity (especially morbid obesity [BMI≥40 kg/m²]) and diabetes (DM; double that in whites); lesser leisure-time physical activity; lower intake of fruits and vegetables, and lesser intake of DASH-type diets (to which they are more responsive than whites).

Despite the higher burden of CVD in AA, the literature on risk prediction of CHF (in particular HFrEF and HFpEF CHF) in this population is very limited. Thus, the prevention of CHF in AA is challenged by fundamental gaps in our knowledge in this high-risk group that include limited data on variations in CHF risk over the short-term (5 years), intermediate term (10 years) and long-term (lifetime risk). These critical gap in knowledge mostly likely stem from the paucity of longitudinal community-based AA cohorts that are designed to address the aforementioned questions. The current
application will bridge this gap using data from the ARIC Study accompanied by mentoring of minority young scientists.

5. **Main Hypothesis/Study Questions:**

**Specific Aim:** To create parsimonious 5-year, 10-year and long-term CVD risk prediction algorithms in AA. Using data from ARIC, we will perform multivariable analyses to relate age, sex, body mass index, systolic blood pressure, diastolic blood pressure, smoking, diabetes, and lipids and subclinical disease measures (echo LVH, LV ejection fraction, carotid IMT, ABI and estimated GFR) to incidence of CHF and specifically HFrEF and HFrEF.

**Hypothesis:** We hypothesize that subclinical disease measures will incrementally predict CVD risk over standard CVD risk factors both in the short-term and intermediate term time horizon. We further postulate that there will be variation in the most parsimonious model for HFrEF versus HFrEF and for short term versus long-term risk of incident CHF.

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).**

**Risk Factors from ARIC Visit 3**

**ARIC Visit 3**

Risk Factors = age, sex, diabetes, hypertension, lipid profile, fasting glucose, systolic and diastolic BP, BMI, total cholesterol, HDL, LDL, waist circumference, premenopausal status, lipid lowering meds, antihypertensive meds, hormone replacement medications, diet, urinary Na from Visit 3.

Echo parameters = LV mass, LV ejection fraction and LV fractional shortening; Carotid IMT, ABI, estimated GFR

Prevalent heart failure will be defined hospitalization with ICD-9 code for HF (428.x) listed at discharge between visit 1 and 3 (n=34).

**Incident Events**

Adjudicated Events CHF events from 1993 forward

**Statistical Analysis:** We will use multivariable Cox proportional-hazards regression to investigate the predictive ability of standard risk factors (age, systolic blood pressure, total cholesterol to HDL cholesterol ratio, e-GFR, smoking, diabetes mellitus, anti-
hypertensive medications), and subclinical diseases (ABI, LVMII, EF and Carotid IMT) of 10-year risk of the first CHF event. All continuous variables will be natural logarithmically-transformed and then standardized within sex to account for their skewed distributions and for sex-specific differences.

After checking and confirming requirements for the assumption of proportionality of hazards, we will use the likelihood ratio test to compare the model with each set of predictors (traditional risk factors and subclinical diseases) i.e., full models versus the reduced model (i.e., model with traditional risk factors only). The difference (ΔG²) in -2 log likelihood between the full and the reduced model will be distributed as a chi-square with k degrees of freedom (where k is the number of subclinical disease markers). A p-value less than 0.05 will indicate evidence against the reduced model.

To test the utility of the selected model in risk prediction, we will perform analysis of the overall C statistic according to Pencina et al. The overall C statistic is used to describe the performance of a given model applied to the population under study. We will also used Net Reclassification Improvement (NRI) to investigate the incremental predictive value of each selected predictor.

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 ICTDER 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.csc.c.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)?
None MPs that have been proposed are related to development of predictive models of HFrEF and HFpEF based on currently proposed subclinical disease markers in African Americans.

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

   _X_ A. primarily the result of an ancillary study: 2012.25 “Validation of Heart Failure Hospitalizations in African Americans with Echocardiography.

   ____ 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/

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.cscc.unc.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


