ARIC Manuscript Proposal # 1537

1.a. Full Title:  Echocardiographic Predictors of Incident CHF and Cardiovascular Events in African Americans

b. Abbreviated Title (Length 26 characters):  Echo and incident CHF in AA

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ERF

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3. Timeline:
Following approval of this manuscript by the ARIC Publications Committee this work will lead to manuscript within 6-12 months.
4. **Rationale:**

Hospital discharges for heart failure (HF) rose from 399,000 in 1979 to 1,099,000 in 2004, an increase of 175%. Data from Ambulatory Care Visits to Physician Offices, Hospital Outpatient Departments, and Emergency Departments: US, 1999 to 2000, showed the number of visits for CHF was 3.4 million. The estimated direct and indirect cost of HF in the United States for 2007 is $33.2 billion. In 2001, $4.0 billion ($5912 per discharge) was paid to Medicare beneficiaries for HF. (1)

There are racial differences in the incident rates of HF and the death rates for HF in the United States. The annual rates per 1000 population of new HF events for white men are 15.2 for those between ages 65 and 74 years, 31.7 for those between ages 75 and 84 years, and 65.2 for those ages 85 and older. For white women in the same age groups the rates are 8.2, 19.8, and 45.6, respectively. For black men the rates are 16.9, 25.5, and 50.6, and for black women the rates are 14.2, 25.5, and 44.0, respectively. Additionally, incident heart failure before 50 years of age is substantially more common among blacks than among whites. (2) Hypertension, obesity, and systolic dysfunction that are present before a person is 35 years of age are important antecedents that may be targets for the prevention of heart failure. The 2004 overall death rate for HF was 19.1. Death rates were 20.3 for white males, 22.9 for black males, 18.3 for white females, and 19.0 for black females.

Among the clinical presentations of cardiovascular (CV) disease attributable to CV risk factors and their combination, HF has a substantial relevance, due to the increasing incidence, which is related to both the reduced mortality for myocardial infarction (MI) and the aging of population. (3) (If interested in saving space, can summarize the above 3 paragraphs more concisely as the focus of your rationale is LV mass as your "predictor variable")

Independent of traditional risk factors such as BP, BMI, and diabetes, excess LV mass might portend impending HF. (4) Excess of LV mass appears to be associated with a cluster of geometric and functional abnormalities, including concentric LV geometry, reduced LV chamber function, depressed midwall shortening, and prolonged LV relaxation. The key feature of the geometric–functional abnormality appears to be echocardiographic increase in myocardial relative wall thickness. Development of LV concentric geometry tends to preserve pump function despite depressed intrinsic wall mechanics, through both direct mechanisms related to the organization of myocardial fibers (6) and geometric modifications maintaining myocardial afterload near normal.

These progressive geometric and functional alterations in myocardial structure with increasing severity of LV hypertrophy suggest that the increase in LV mass is not necessarily due to real muscle hypertrophy, since the fibrosis component also increases and correlates with the degree of diastolic dysfunction. (7, 8) Although an extensive analysis of diastolic dysfunction has not been done, the presence of increasing left atrial diameter in the final predictive model strongly suggests chronic, severe abnormality of LV filling properties. (9) Both LV hypertrophy and LV systolic function, even within the range of normality, have been shown to be important independent predictors for incident HF.

African Americans have a disproportionately higher incidence of echocardiographic LV hypertrophy compared to European Americans. In previous studies we have shown that LV structure, geometry and function predict all-cause mortality in this population in the ARIC study, how these echocardiographic parameters specifically predict incident HF and cardiovascular mortality in African Americans is not completely clear. We will use recently collected information on incident HF and cardiovascular events in the Jackson Cohort of ARIC population to investigate this question.

5. **Main Hypothesis/Study Questions:**
The study questions below will explore whether echo variables of LV structure and function are predictors of incident heart failure and cardiovascular events, controlling for covariates for incident heart failure:

1. To estimate the association of echo LV wall thickness and LV mass with incident heart failure
2. To estimate the association of echo LV geometry with incident heart failure
3. To estimate the association of echo parameters of systolic LV function with incident heart failure
4. To estimate the association of echo parameters of diastolic LV function with incident heart failure

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).

The study population for this analysis will be the Jackson cohort participants in the ARIC Study. Those with prevalent HF at baseline will be excluded from this analysis. Prevalent HF is defined as the reported current intake of HF medication at the baseline examination or evidence of manifest HF as defined by the Gothenburg criteria stage 3; in addition, those with missing Gothenburg criteria items needed to define prevalent HF will be excluded.

Echo variables will be based on echocardiograms performed in ARIC Jackson participants in Examination 3 between 1993-1996.

Incident HF will be defined according to two time periods. For cases occurring prior to and through December 31, 2004, incident HF is defined as the first HF hospitalization or as the underlying cause of death, identified through hospital discharge codes (ICD-9 428) and from death certificate codes from annual listings from state vital records offices (428 and I50). For cases occurring January 1, 2005 onward, incident HF will also be defined as the first HF hospitalization confirmed as physician review using “ARIC criteria”; these will include acute decompensated HF and chronic stable HF.

The follow-up period will be from the time of the echocardiogram to the time of the event/outcome or the date of censoring. Event/outcome variables will include incident CHF and cardiovascular mortality (death due to CHF, CHD, MI or stroke). Independent (predictor) variables will include: LV mass index (continuous), LV geometry (4 groups: normal, concentric remodeling, eccentric hypertrophy, and concentric hypertrophy), LV ejection fraction (dichotomous), LV fractional shortening (dichotomous), and LV impaired relaxation (3 groups). We will calculate, by predictor variable group, crude and age/sex-adjusted event/outcome rates per 100 (or 1,000) person-years using Poisson regression. We will also conduct, by predictor variable group, Kaplan-Meier survival analysis to compare unadjusted survival curves for each predictor group, and Cox proportional hazard (PH) regression analysis to determine event/outcome hazard ratios and 95% CIs.
Clinical variables that will be considered for adjustment in the Cox PH models include: sex, SBP, DBP, BMI, waist circumference, CRP, fibrinogen levels, diabetes, fasting insulin levels (if present), creatinine, GFR by MDRD, cholesterol status, hypertension medications, lipid lowering medicines, HRT, Aspirin therapy, Interaction terms with hypertension status, BMI, and prevalent and/or incident MI will be tested, and appropriate sub-group analyses done as required. In secondary analysis, persons with incident HF will be separated into 2 groups (preserved vs. not preserved EF) in those with that data.

7. a. Will the data be used for non-CVD analysis in this manuscript?  No

8.a. Will the DNA data be used in this manuscript?  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.

No current overlaps

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)?

(Would list & mention that these authors are part of this proposal – so you might add Sunil Agarwal after all):
MS # 1475- Hypertension, left ventricular hypertrophy, and risk of incident hospitalized heart failure: The ARIC study
MS # 1516 (Saul Blecker’s proposal).

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.

2. Kirsten Bibbins-Domingo, Ph.D., M.D., Mark J. Pletcher, M.D., M.P.H., Feng Lin, M.S., Eric Vittinghoff, Ph.D., Julius M. Gardin, M.D., Alexander Arynchyn, M.D., Cora E. Lewis, M.D., O. Dale Williams, Ph.D., and Stephen B. Hulley, M.D., M.P.H. Racial Differences in Incident Heart Failure Among Young Adults. *n engl j med* 360;12 nejm.org march 19, 2009


