ARIC Manuscript Proposal # 1475

PC Reviewed: 2/10/09  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Hypertension, left ventricular hypertrophy, and risk of incident hospitalized heart failure: The ARIC study

b. Abbreviated Title (Length 26 characters): Hypertension, LVH, and Heart failure

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:
   Following approval of this manuscript by the ARIC Publications Committee this work will lead to manuscript(s) within 15 months.
4. **Rationale:**
Heart Failure (HF) is a major public health problem in the US [1]. While it has a grim prognosis (30% mortality at one year)[2], HF treatment costs exceed those for both coronary artery disease and cancer combined and require about 5.4% of the total US health care cost [3]. Hypertension (HTN), a common HF precursor, is even more common, affecting 1 in 3 adults in the U.S., and more prevalent with an earlier onset among African Americans [4]. Despite the well known association between HTN and coronary artery disease (CAD), few population based studies have shown an association between HTN and incident HF [5-8].

High blood pressure (BP) is strongly associated with CAD[4]. Also, high BP is associated with incident HF among patients with CAD [9]. However, high blood pressure may also have direct effect on myocardium, apart from its role in atherosclerosis and CAD. In large inpatient databases, systolic blood pressure was an independent predictor of morbidity and mortality in patients with HF, even those preserved systolic function[10]. Further, a recent analysis from the Framingham cohort showed that antecedent blood pressure and body mass index (BMI) were associated with incident HF despite adjustment for recent BP and BMI[11]. Also, patients who have HF with preserved ejection fraction (HFpEF or diastolic HF) tend to be older, female, and have a history of HTN [12]. These findings point to long-term cumulative adverse effects of high blood pressure on the heart.

Left ventricular hypertrophy (LVH) is an adverse consequence of long-term high blood pressure and may lead to diastolic dysfunction and then HF. Interestingly, reduction in LVH (defined electrocardiographically by the Cornell criteria) during antihypertensive therapy is associated with fewer hospitalizations for HF, independent of blood pressure lowering, treatment method, and other risk factors for HF[13].

To date little (if any) information of this kind is available for African Americans, a population group that manifests a heavy burden of HF and its associated mortality. The ARIC cohort provides a unique opportunity to further understand more about the relationships between systolic and diastolic blood pressure, pulse pressure, left ventricular hypertrophy, and incident hospitalized heart failure among both blacks and whites. This cohort will provide opportunity to study the above relations in a CAD-free sub-cohort.

5. **Main Hypothesis/Study Questions:**
1. High blood pressure, as defined below, is associated with incident hospitalized HF among both blacks and white in the ARIC cohort.
   - Hypertension will be defined using JNC VII criteria[14]. This will include isolated systolic hypertension (based on measured systolic blood pressure) and isolated diastolic hypertension (based on measured diastolic blood pressure).
   - Uncontrolled hypertension will be defined as either SBP ≥140 mm Hg or DBP ≥90 mm Hg in participants answering “yes” to questions of self-reported hypertension and/or previous treatment of hypertension.

2. The association in 1 will exist even among those without prevalent or incident coronary heart disease. The association in the CHD-free sub-cohort will be
stronger among those who are older, obese, or have renal impairment as these factors are more strongly linked with diastolic dysfunction.

3. Left ventricular mass, as defined below, will be associated with incident hospitalized HF independent of measured blood pressure at baseline.
   - Cornell voltage determined left ventricular hypertrophy (>32 mV in men, >28 mm in women)
   - ECG determined continuous Cornell voltage

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).

Those with prevalent HF at baseline will be excluded for the main analysis. Prevalent HF is defined as the reported current intake of HF medication at the baseline examination (n = 83) or evidence of manifest HF as defined by the Gothenburg criteria stage 3 (n = 669), which require the presence of specific cardiac and pulmonary symptoms as well as medical treatment of HF[15]. In addition, 289 will be excluded due to the missing criteria needed to define prevalent HF. Incident HF was defined as the first HF hospitalization or HF coded as the underlying cause of death, identified through hospital records provided by all hospitals in the ARIC study areas and from death certificate codes from annual listings from state vital records offices. Hospitalizations were coded as heart failure (428) using the International Classification of Diseases Code, Ninth Revision (ICD-9), and deaths were coded as HF (428 and I50) using the ICD-9 and ICD-10. By January 1st, 2003, 1193 study participants met these incident HF criteria. Analyses for this study will include additional incident HF events i.e., through 2005 using the same criteria.

Cox proportional hazards regression models will be used to assess the hypotheses. For subset analysis involving a CAD-free cohort, individuals with baseline or incident CHD prior to incident CHF will be excluded. Proportional hazard assumptions will be examined for the main exposure and all covariates with log – log curves and time interaction terms (Cox test). Linearity of log (HR) will be examined. We will examine statistical interaction in hazard ratios with age, gender, race, BMI, and renal dysfunction.

In addition, since high blood pressure and other potential risk factors for HF (such as coronary artery disease, diabetes, obesity) can develop over time, secondary analyses will incorporate the exposure variables as time-varying in Cox proportional hazards models.

Lastly, we will estimate the population attributable fraction of heart failure due to hypertension.

Variables requested:
Visit 1: Blood pressure measures, medication, demographics (age, gender, race, center), Socio economic indicators (education and income), anthropometric measures (height, BMI, waist circumference, waist-hip ratio), comorbidites and CVD risk factors
(smoking, COPD, T2DM, hypertension, LDL-cholesterol, HDL cholesterol), Gothenburg score, prevalent CAD.

**Visit 2 to visit 4:** Blood pressure measurements, medication use, LDL cholesterol, HDL cholesterol, fasting blood sugar, T2DM, BMI, smoking status

**Follow up through 2005:** incident CHD, incident hospitalized HF

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.

There is slight overlap with a sub-aim of existing proposal MP#1342 (The preventable burden of heart failure due to obesity and hypertension). While MP#1342 will try to estimate an attributable fraction due to clinically defined hypertension, this proposal will examine a causal association of hypertension and left ventricular hypertrophy with heart failure. The lead author (Laura Loehr) is a co-author of this proposal and has agreed with this proposal.

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)?

MP#1342 The preventable burden of heart failure due to obesity and hypertension.

(Please see above)

There are other proposals looking at other risk factors of heart failure as listed below. These proposals include hypertension as a potential confounder in their multivariable models but are not otherwise focused on hypertension as a risk factor for heart failure.

MP#922 Alcohol consumption and risk of congestive heart failure
MP#890B Plasma Fatty Acid Composition and Incidence of Heart Failure in Middle Aged Adults
MP#1118 Kidney Function as a Risk Factor for Incident Heart Failure
MP#1125 Diabetes, obesity and insulin resistance as risk factors for incident hospitalized HF
MP#1144 The Obesity Paradox in Heart Failure.
MP#1160 Life Course Socioeconomic Exposures and Heart Failure.
MP#1164 Hemoglobin A1c as a Risk Factor for HF Hospitalization among Persons with Diabetes.
MP#1197 Albuminuria as a Predictor of Incident Heart Failure Hospitalization and Mortality.
MP#1232 ECG Abnormalities Preceding Heart Failure: Estimation and Prediction
MP#1276 Exhaustion and risk for congestive heart failure.
MP#1377 Relationship between pulmonary disease, lung function and incident hospitalized heart failure

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

12. The authors are aware of proposal expiration at three years, if incomplete.

References