ARIC Manuscript Proposal #2024

PC Reviewed: 10/9/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Prehypertension (Pre-HTN) is associated with abnormalities of Cardiac Structure and Function

b. Abbreviated Title (Length 26 characters): Pre-HTN and echo parameters.

2. Writing Group:

Writing group members: Angela B S Santos, Natalie Bello, Deepak Gupta, Amil M. Shah, Susan Cheng, Scott D. Solomon. Others welcome.

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

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3. Timeline: Analysis will begin following proposal approval. Anticipating completion of echocardiography of ARIC Visit 5 cohort in 2013, a manuscript will be completed within 6 months of the date.

4. Rationale:

Prehypertension (Pre-HTN) is defined as a blood pressure ranging from 120-139mmHg systolic and/or 80-89mmHg diastolic by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JVC-7).[1] The prevalence of Pre-HTN was estimated to be 31% among US adults [2] and even higher globally[3]. Its prevalence is higher in males and African-Americans, and increases with age[456]. This new category of blood pressure calls attention to a growing recognition of the cardiovascular risk associated with levels of blood pressure which were previously thought to be normal. In 2001, Vasan *et al* showed, in the Framingham Heart Study, that Pre-HTN was associated with an adjusted hazard ratio of 2.5 in women and 1.6 in men for cardiovascular disease[7]. In the ARIC Study, Kshirsagar *et al* found a relative risk of 2.33 for Pre-HTN compared to optimal blood pressure (<120/80mmHg) in the risk of cardiovascular disease and this risk was even higher in African-Americans, individuals with diabetes, LDL 100-129mg/dL or BMI>30kg/m^2 [8].

Prehypertension is also related to end organ damage and changes in cardiac structure and function. Increased left ventricular mass has been described in populations with pre-HTN[9,10,11],even in subjects as young as 14 years of age.[12], as well as impaired left ventricular diastolic function[10] Akturk *et al* demonstrated prehypertensives have increased LA volume and active systolic function despite reduced passive LA systolic function, while traditional echocardiographic parameters, such as pulse wave Doppler and tissue Doppler, did not demonstrate these differences[13]. This finding may reflect an early increase in left ventricular stiffness in prehypertensives. Di Bello *et al* also showed that longitudinal 2D strain was significantly lower in those with prehypertension compared to normotensive subjects, while circumferential and radial strain was preserved, which may be related to early abnormalities in subendocardial function[14].

The Atherosclerosis Risk in Communities (ARIC) Study presents a great opportunity to identify the cardiac repercussions of pre-HTN in a diverse population sample. Understanding the impact of pre-HTN on left ventricular geometry, diastolic function, and early parameters of systolic function may help to better define prevention and treatment strategies for this condition in the future.

5. Main Hypothesis/Study Questions:

The primary objective is to define the impact of pre-HTN compared to optimal blood pressure on cardiac structure and function.

Hypothesis 1. Pre-HTN is associated with increased left ventricular (LV) mass, more frequent diastolic dysfunction, and impaired myocardial systolic function and deformation in the longitudinal plane.

Hypothesis 2. There are racial differences in the adaptive responses to pre-HTN with African-American showing more pronounced alterations in cardiac structure and function.

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 cross sectional study of ARIC cohort participants during visit 5 (2011-2012) who have acceptable image quality for analysis. Participants will be excluded if they have hypertension (defined as systolic blood pressure (BP) ≥140 or diastolic BP ≥90 or are taking antihypertensive medications. Additional exclusion criteria include impairment of left ventricular systolic function (ejection fraction<50%), congestive heart failure, significant valvular disease, cardiomyopathy or coronary disease, and race other than black or white.

Variables to be evaluated

Dependent variables: The primary dependent (outcome) variables of interest will include: 1) left ventricular (LV) mass (primary measure of LV structure), 2) tissue Doppler imaging E prime (primary measure of LV diastolic function), 3) speckle-tracking based longitudinal strain (primary measure of LV systolic function). In secondary analyses, we will also consider the following measures of LV structure and function: LV relative wall thickness, left atrial volume, E/A ratio, deceleration time, LVEF, circumferential strain, and radial strain

Independent variables: The primary independent (predictor) variables will be measures of blood pressure (in the absence of hypertension). We will consider blood pressure measures taken during the clinic visit primarily (and blood pressure measures at the time of echocardiogram in secondary analyses). Blood pressure measures will be analyzed as both continuous variable and ordinal categorical variable. For categorical analyses, blood pressure will be categorized as: high normal blood pressure (130mmHg≤ systolic BP<140mmHg or 85mmHg ≤diastolic BP <90mmHg), normal blood pressure (120mmHg≤ systolic BP<130mmHg or 80mmHg<diastolic BP 85 mmHg) and optimal normal blood pressure (systolic BP<120mmHg and diastolic BP < 80mmHg). Pre-HTN will be represented by the two former categories.

Analytical approach:

Continuous normally distributed data will be displayed as mean and standard deviation and continuous non-normally distributed data will be displayed as median and interquartile range. Categorical data will be shown as a total sample and proportion. Associations of blood pressure and primary echocardiographic outcomes will be evaluated first using unadjusted linear regression. The primary independent variables of interest will include standard continuous BP variables (SBP, DBP, MAP, and PP) and then, in separate models, the categorical BP variables defined above: high-normal, normal, and optimal (referent group). We will perform multivariable linear regression analyses adjusting for the following covariates: age, gender, heart rate, height, weight, body mass index, diabetes, dyslipidemia, creatinine, total/HDL cholesterol, c-reactive protein, high-sensitivity troponin, and b-type natriuretic peptide. In secondary analyses, the same analyses will be performed for the secondary echocardiographic outcome variables. We will test for interaction among LV structure and systolic/diastolic function and race. P values<0.05 will be considered significant.

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

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)?

Abhijit V Kshirsagar, Myra Carpenter, Heejung Bang, Sharon Wyatt RN, Romulo E Colindres. **The Natural Hystory of Pre-Hypertension**. Manuscript proposal #998 April, 2004.

Abhijit V Kshirsagar, Myra Carpenter, Heejung Bang, Sharon Wyatt RN, Romulo E Colindres. **Blood pressure usually considered normal is associated with an elevated risk of cardiovascular disease**. Am J Med. 2006 Feb;119(2):133-41.

Hui Han, Herman Taylor Jr, Dan Jones, Jun Pan, Bob Garrison.**The impact of treatment and adequate control of blood pressure for hypertension on left ventricular hypertrophy .** Manuscript proposal #947 July, 2003.

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/

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.

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