ARIC Manuscript Proposal #1821

PC Reviewed: 10/11/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Relation of Different Blood Pressure Indices with Risk of Different Cardiovascular Events in the ARIC Cohort

b. Abbreviated Title (Length 26 characters):

BP indices and CV risk

2. Writing Group:
Writing group members:

Susan Cheng, Hanyu Ni, Amil Shah, A. Richey Sharrett, Hicham Skali, Scott Solomon, Madoka Takeuchi, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __SC__

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3. Timeline: Analyses to begin Fall 2011.
A manuscript draft is expected during Winter 2011 / Spring 2012.

4. Rationale:

Elevated blood pressure (BP) remains a widely prevalent and significant contributor to cardiovascular risk.[1] Recent studies indicate that the different components of BP – including systolic (SBP), diastolic (DBP), pulse pressure (PP), and mean arterial pressure (MAP) – provide complementary information regarding the hemodynamic alterations associated with various forms of hypertension and their associated risk for cardiovascular events.[2,3] In particular, PP is considered a measure of pulsatile load and most representative of larger artery stiffness; MAP, on the other hand, is considered a measure of steady state load and most representative of peripheral arterial resistance.[2,4] Thus, it has been hypothesized that the different indices of BP elevation may be associated to varying degrees with different cardiovascular outcomes, including coronary heart disease (CHD), heart failure (HF), and stroke.[5,6] However, evidence to date regarding the extent to which individual BP indices are variably associated with select cardiovascular outcomes has been conflicting.[2,7,8] The inconsistency of findings from prior investigations may be due to several reasons, including small-sized and/or referral samples, the fact that BP indices are known to substantially change with advancing age,[9-11] baseline differences in BP indices between racial/ethnic groups,[12] and limited event rates for select cardiovascular outcomes. Thus, we propose to evaluate the extent to which baseline SBP, DBP, MAP, and PP are associated with the incidence of CHD, HF, stroke, and cardiovascular death in a large community-based cohort. Prior literature indicates that baseline BP indices vary across demographic groups; for example, elevation in DBP and MAP is more common in younger adults whereas elevation in SBP and PP is more common in older adults.[9] Thus, we also propose to assess the degree to which age, sex, and race influence the magnitude of associations between select BP indices and cardiovascular outcomes.

5. Main Hypothesis/Study Questions:

Our main hypothesis is that elevations in different BP indices are most strongly related to different cardiovascular outcomes. Our specific hypotheses are:

1) Elevated PP, compared to other BP indices, is a stronger predictor of HF (in the absence of prior CHD).

2) Elevated PP, compared to other BP indices, is a stronger predictor of stroke.

3) Incidence of CHD is more strongly associated with baseline elevated DBP (and MAP) in younger age, but more strongly associated with baseline elevated SBP (and PP) in older age.

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 sample will include individuals who attended ARIC examination Visit 1 and were free of cardiovascular disease (CHD, HF, or prior stroke) at the time of this 'baseline' examination. Data analysis will focus on baseline BP indices as the main exposures of interest.

Incidence Analyses

We will compare unadjusted incidence rates for each outcome (new-onset CHD, HF, and stroke) for individuals in the upper (>75th percentile) compared to lower quartile (<25th percentile) of each BP measure at baseline. We will then repeat these analyses with adjustment for the following traditional cardiovascular risk factors: baseline age, sex, body mass index (BMI), cholesterol levels (total, HDL, LDL), presence versus absence of diabetes, and smoking status. Electrocardiographic evidence of left ventricular hypertrophy (LVH) will be included as a covariate for incident HF. Resting heart rate will be included in analyses that include PP.

Regression Analyses

Independent variables. The primary predictor variables of interest will include baseline SBP, DBP, MAP, and PP. Untreated BP values for individuals taking anti-hypertensive medications at baseline will be imputed using an established conventional method (i.e. add 10 mmHg to SBP and 5 mmHg to DBP for each individual taking anti-hypertensive medication at the time of BP measurement). Both linear and quadratic terms for each BP measure will be considered. Covariates of interest will include the following traditional cardiovascular risk factors: baseline age, sex, body mass index (BMI), cholesterol levels (total, HDL, LDL), presence versus absence of diabetes, and smoking status. Electrocardiographic evidence of left ventricular hypertrophy (LVH) will be included as a covariate for models of incident HF. Resting heart rate will be included in analyses that include PP as a covariate.

Dependent variables. The primary dependent variables of interest will include incident CHD, HF, stroke, and cardiovascular death (separate models for each endpoint, in addition to the model using the combined endpoint). Analyses of HF will be performed excluding individuals who developed CHD prior to the onset of incident HF. We will use multivariable Cox regression analyses to examine the association of the different BP measures (individually and together) with each endpoint while adjusting for traditional cardiovascular risk factors.

Analytical approach. Because BP measures are known to correlate with each other, we

will perform multivariable analyses of BP predictor variables using an approach based on previously established methods.[2,7] Specifically, we will evaluate the predictive power of each BP measure versus each of the other BP measures using the -2 log-likelihood difference between multivariable-adjusted models (to assess the increased variance explained by each measure [linear term only] or pair of measures [linear and quadratic term]). The relative strength of SBP compared with each of the other BP variables will be assessed by comparing the -2 log-likelihood value for models with and without the variable. For example, the predictive power of MAP and PP with respect to the HF outcome will be compared by constructing 3 models: Model 1 will include linear terms for MAP and PP (and quadratic terms, if significant) along with traditional HF risk factors; Model 2 will include the same variables as Model 1 but exclude PP; and, Model 3 will include the same variables as Model 1 but exclude MAP. Models 2 and 3 will be compared to Model 1 to determine the -2 log-likelihood difference for MAP and PP, respectively, with a larger difference indicating better predictive power.

Secondary analyses. For each BP measure demonstrating a significant association with a cardiovascular outcome, we will test for effect modification by age, sex, and race. In secondary analyses, we will also repeat all models above in individuals with BP measurements available at ARIC visits subsequent to the baseline examination (up to visit 4), where each BP measure will be treated as a time-dependent covariate.

Limitations and challenges. All BP indices are known to be inter-correlated to some extent. Therefore, the main analyses will be conducted according to the pre-specified plan, briefly described above, which involves using a stepwise approach to evaluate the relative association of each BP measure with the outcome of interest, with respect to the referent BP measures (i.e. SBP). Because BP indices may have non-linear associations with the outcomes of interest, we will also consider quadratic terms for each BP measure.

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

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)?

MS# 513 (Chambless) Association of arterial stiffness and cerebrovascular diseases.

MS# 723 (Din-Dzietham) Arterial Stiffness is greater in African Americans than in whites: Evidence from the Forsyth County, North Carolina, ARIC cohort. Am J Hypertens 2004;17:304-313.

MS #865 (Kshirsagar) Blood pressure usually considered normal is associated with an elevated risk of cardiovascular disease. Am J Med 2006;119:133-41.

MS #1461 (Yang) The association of arterial stiffness with incident cardiovascular disease – an analysis from the ARIC Study

MS #1806 (Yang) The association between arterial stiffness and incident heart failure and microvascular disease – an analysis from the ARIC Study

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.

References

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