ARIC Manuscript Proposal # 1821

PC Reviewed: 7/12/11	**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 Community

b. Abbreviated Title (Length 26 characters):

BP indices and CV risk

2. Writing Group:
Writing group members:

Susan Cheng, Amil Shah, 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_ **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Analyses to begin Summer 2011. A manuscript draft is expected during Winter 2011.

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 artery disease (CAD), heart failure (HF), and stroke. However, evidence to date regarding the extent to which individual BP indices are variably associated with select cardiovascular outcomes has been conflicting.[2, 5, 6] 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,[7-9] baseline differences in BP indices between racial/ethnic groups,[10] and limited event rates for select cardiovascular outcomes. Thus, we propose to evaluate the extent to which SBP, DBP, MAP, and PP are associated with the incidence of CAD, HF, stroke, and cardiovascular death in a large community-based cohort. Because baseline BP indices are known to vary across demographic groups, 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 different BP indices are most strongly related to different cardiovascular outcomes. Our specific hypotheses are:

1) A history of elevated PP, compared to other BP indices, is a stronger predictor of HF (particularly in the absence of prior CAD).

2) A history of elevated MAP, compared to other BP indices, is a stronger predictor of stroke.

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

6. Data (variables, time window, source, inclusions/exclusions):

The study sample will include individuals who attended at least one ARIC examination (beginning with Visit 1) and were free of cardiovascular disease (CAD, HF, or prior stroke) at the time of this 'baseline' examination. Data analysis will take place in two stages, the first focusing on baseline BP indices and the second focusing on antecedent BP indices:

Baseline BP indices. The primary predictor variables of interest will include SBP, DBP, MAP, and PP. Covariates of interest will include baseline age, sex, body mass index (BMI), cholesterol levels (total, HDL, LDL), presence versus absence of diabetes, and smoking status. We will use multivariable Cox regression analyses to examine the association of the different BP measures (individually and together) with the incidence of CAD, HF, stroke, or cardiovascular death (separate model for each endpoint, in addition to a model using the combined endpoint), while adjusting for traditional cardiovascular risk factors. For each BP measure demonstrating a significant association with a cardiovascular outcome, we will test for effect modification by age (<60 versus ≥60 years), sex, and race. In secondary analyses, untreated BP values for individuals taking anti-hypertensive medications at baseline will be imputed using a conventional method.

Antecedent BP indices. The primary predictor variables of interest will include 'trajectories' of SBP, DBP, MAP, and PP based on antecedent measures. The 'trajectory' of each BP measure will be determined using change (absolute and percent difference) and time-averaged values of each measure collected from individuals attending at least 2 consecutive examinations. We will also consider using multi-level modeling approaches to defining BP trajectories. We will use multivariable Cox regression analyses to examine the association of the BP trajectories (individually and together) with the incidence of CAD, HF, stroke, or cardiovascular death (separate model for each endpoint, in addition to a model using the combined endpoint), while adjusting for traditional cardiovascular risk factors that include the relevant baseline BP measure(s). For each BP trajectory demonstrating a significant association with a cardiovascular outcome, we will test for effect modification by age (<60 versus ≥60 years), sex, and race. In secondary analyses, untreated BP values for individuals taking anti-hypertensive medications at baseline will be imputed using a conventional method.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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# 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.

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
___ 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

1. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S,

Wong N, Wylie-Rosett J, Hong Y. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2009;119:e21-181.

2. Franklin SS, Lopez VA, Wong ND, Mitchell GF, Larson MG, Vasan RS, Levy D. Single versus combined blood pressure components and risk for cardiovascular disease: the Framingham Heart Study. *Circulation.* 2009;119:243-250.

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5. Bangalore S, Messerli FH, Franklin SS, Mancia G, Champion A, Pepine CJ. Pulse pressure and risk of cardiovascular outcomes in patients with hypertension and coronary artery disease: an INternational VErapamil SR-trandolapril STudy (INVEST) analysis. *Eur Heart J.* 2009;30:1395-1401.

6. Anderson RD, Sizemore BC, Barrow GM, Johnson BD, Merz CN, Sopko G, von Mering GO, Handberg EM, Nichols WW, Pepine CJ. Pulse pressure and adverse outcomes in women: a report from the Women's Ischemia Syndrome Evaluation (WISE). *Am J Hypertens.* 2008;21:1224-1230.

7. Franklin SS, Gustin Wt, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation.* 1997;96:308-315.

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9. Fields LE, Burt VL, Cutler JA, Hughes J, Roccella EJ, Sorlie P. The burden of adult hypertension in the United States 1999 to 2000: a rising tide. *Hypertension.* 2004;44:398-404.

10. Din-Dzietham R, Couper D, Evans G, Arnett DK, Jones DW. 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.