

ARIC Manuscript Proposal #1961

PC Reviewed: 7/10/12
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Variability of BP and its impact on CHD, stroke, and Heart Failure risk prediction in the ARIC study

b. Abbreviated Title (Length 26 characters): BP variation impact on outcomes

2. Writing Group:

Writing Group Members:

Abayomi N. Ogunwale MD
Vijay Nambi MD PhD
Alanna C. Morrison, PhD
Addison Taylor MD
Rebecca Gottesman MD
Eric Yang MD
Gerardo Heiss MD
Wei Peng, PhD
Salim S Virani MD PhD
Eric Boerwinkle PhD
Christie Ballantyne MD

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

Firstauthor: Abayomi N. Ogunwale
Address: Abayomi N. Ogunwale
School of Public Health,
University of Texas, Houston Campus
1200 Herman Pressler Street
Houston, TX 77030
Phone: 832 245 1207
Abayomi.N.Ogunwale@uth.tmc.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):

Vijay Nambi MD

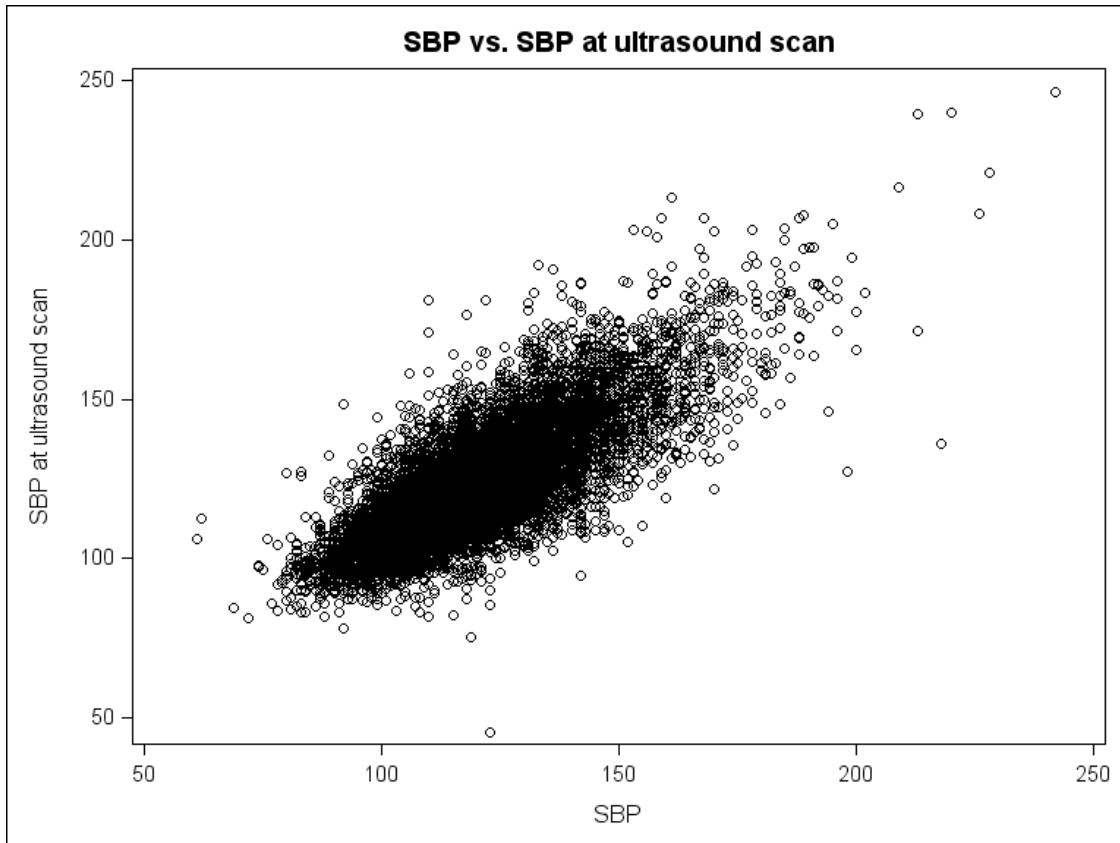
Address: Vijay Nambi
Baylor College of Medicine,
6565 Fannin Street,
MS A601/ STE B160
Houston, TX 77030
Phone: 713-798-7545
Fax: 713-798-7885
E-mail: vnambi@bcm.tmc.edu

3. Timeline: Analysis to start as soon as approval is obtained. Manuscript is to be prepared as soon as analyses are completed. Analysis and manuscript preparation will take place within 1 year from approval of the proposal.

4. Rationale: Blood pressure (BP) is used in all coronary heart disease (CHD) and stroke risk prediction models. The association of BP with stroke is stronger than its association with CHD (R.Collins et al 1994). Often the BP used in risk prediction models is a sitting BP reading obtained at a clinical exam.

BP values change throughout the day in response to position and other factors (Parati G et al., 1998). Also, recent studies suggest that variability of systolic BP is a strong predictor of stroke, heart failure, angina, and myocardial infarction, independent of mean BP (Rothwell et al. 2010). Whether BP measured under other postural conditions, and whether the difference in BP during the day are more predictive of cardiovascular risk –than a singular sitting reading- has not been adequately described.

In ARIC visit 1 and 2, BP measurements were available for most subjects at three time points: (1) a sitting measurement using a random zero mercury manometer, (2) BP measurements performed during ultrasound imaging in the recumbent position, and (3) measurement of BP in the standing position. The measurements performed while lying down and standing were in the same arm using a Dinamap system. Additionally, at each of these time points, several BP recordings were performed (thrice when sitting, once every 5 minutes during the ultrasound imaging, and every 20 seconds when standing). As part of the analysis for MS1461, we examined differences between BP readings during a participant's visit and during the ultrasound scan and noted that these were highly correlated, with a mean difference of only 3.2 mmHg. However, substantial within-individual variation was noted (see Figure).



While some differences may be due to measurement error, most may represent changes during the day in response to position or other factors. Irrespective of whether these were measurement errors or true differences, knowledge of their predictive value may have clinical value.

In the Honolulu heart program, BP drop on standing from a supine position (orthostatic hypotension) was found to be an independent significant predictor of mortality among elderly patient (Kamal HM et al. 1998). Similarly, earlier analyses in ARIC have also suggested an association between postural changes in BP and incident hypertension (Rose K et al., 2002), CHD (Nardo CJ, 1999) and stroke (Yatsuya H,2011). However, recumbent BP has not been considered, and only the change in BP was the focus of the previous analyses. We aim to study in further detail which measure of BP, or its changes, are best associated with cardiovascular outcomes and how it affects risk prediction scores.

5. Main Hypothesis/Study Questions:

Hypothesis:

PRIMARY

Sitting, standing and recumbent BP measurements are significant independent predictors of CHD, Heart Failure and stroke. We will

determine which BP measurement improves prediction in established risk scores.

SECONDARY

We will examine the predictive value of the absolute difference, as well as signed difference, between average sitting BP and average standing or recumbent BP measures. We hypothesize that individuals with greater BP variability have worse cardiovascular outcomes.

Questions to be addressed in a stepwise manner:

1. How do sitting, recumbent, and standing BP individually compare with respect to CHD, stroke and heart failure risk predictions? We will describe the AUC for each BP measurement when added to the other traditional risk factors, and then describe the NRI, IDI and goodness of fit. In addition we will compare models incorporating BP readings from each position with each other to determine the number of individuals whose scores would change. CHD risk prediction models will include the ARIC and Framingham CHD risk scores. The ARIC stroke and Heart failure risk scores will also be considered.
2. Do individuals with greater BP variability (as measured by the absolute difference between mean BP recordings; i.e., standing vs. sitting, recumbent vs. sitting, and recumbent vs. standing) have worse cardiovascular outcomes? As an alternative measure of BP variability, we will also examine the predictive value of the estimated variance of repeated BP measures.
3. What is the predictive value of the highest absolute BP change (sitting-recumbent, sitting-standing, recumbent-standing) in risk score calculations for the CHD, stroke, and heart failure outcomes?

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 methodological limitations or challenges if present).

After standard ARIC exclusions, all individuals with prevalent CHD, Heart failure and stroke, as well as individuals with missing covariate data (i.e. covariates required to estimate the ARIC or Framingham risk scores) will be excluded.

Individuals who do not have recumbent or standing BP measurements will also be excluded.

6. Analysis plan:

The following analyses involve only visit 1 data.

1. Identify all clinically relevant variables necessary for the estimation of the ARIC Coronary heart disease Risk Score (ACRS): Recumbent, sitting and standing BP recordings, antihypertensive medication use, total cholesterol, High density lipoprotein C (HDL-C), Sex, smoking status, and age.
2. Examine for any outliers among BP measurements from all three assessments (sitting, standing, and recumbent) and exclude values which are physiologically improbable.
3. Determine a model to assess the variability within sitting, standing, and recumbent BP readings independently, and assess which model significantly (statistically) improves risk score predictions.
4. Estimate the absolute difference and variability between each set of BP readings.

POSITION	ABSOLUTE CHANGE	Signed Difference
Sitting -Recumbent	x	x
Sitting - Standing	x	x
Recumbent -Standing	x	x

5. Complete a descriptive analysis of the changes in BP readings between the different positions
 - a. Define $\Delta SBPA = | \text{Mean SBP Sitting} - \text{Mean SBP Standing} |$
 $\Delta SBPB = | \text{Mean SBP Standing} - \text{Mean SBP Recumbent} |$
 $\Delta SBPC = | \text{Mean SBP Sitting} - \text{Mean SBP Recumbent} |$
 - b. Define same parameters A, B AND C for DBP
 - c. Create frequency histograms of SBPA, SBPB and SBPC for the entire population, and those with available recordings.
 - d. Fit a distribution curve to the histogram.
 - e. Thereafter, summarize $\Delta SBPA$, $\Delta SBPB$ and $\Delta SBPC$ based on race, gender and Hypertension status.
 - f. Use separate regression models to describe the predictors of changes in BP between the various pairs of BP measurements.

6. Using Cox proportional hazards models, describe the estimated CHD risk using the ACRS and FRS (separately) with the sitting BP first, then with the recumbent BP, and then standing BP. Finally add the absolute difference between each pair in BP measurements ($\Delta SBPA$, $\Delta SBPB$ and $\Delta SBPC$) to the Cox models to examine if difference between any pair further adds to the model. Adjustments will need to include anti-hypertensive medication and class.

7. Show a reclassification table for each pair of BP readings: i.e. number of individuals whose risk group changed; calculate the net reclassification index (NRI)

8. Describe using a goodness of fit test as to which model did better when observed and expected risk were compared

9. Again using Cox proportional hazards model, evaluate if the sitting BP, the recumbent BP, standing BP and the difference in BP (absolute value) are associated with CHD even after adjustment for traditional risk factors

10. If absolute changes in BP are associated with incident events, evaluate what absolute changes in BP (we will evaluate >10 , >15 and >20 mmHg) are associated with outcomes

11. Perform additional analysis excluding individuals on anti-hypertensive therapy and then stratified by medication (ACE-inhibitor, diuretic, Beta blocker or calcium channel blocker).

12. Repeat steps 4-11 using incident ischemic stroke as the outcome and the ARIC stroke risk score and similarly incident heart failure as the outcome

12. Determine the variability of BP using all available BP by combining these measures for each individual and determining their standard deviation. Linear mixed model (LMM) will be used to estimate the variance of BP taking into account longitudinal feature of the BP measures and position differences. The standard deviations will then be categorized into quartiles. Examine if BP variability measured in this manner is associated with incident CHD, stroke and heart failure in simple age, gender adjusted models and then in models adjusted for the traditional CHD, Heart failure and stroke risk factors. Additionally the impact of the variability of BP may be different at different levels of baseline BP and this potential interaction will be evaluated as well.

12. Classify the subjects according to BP variability calculated in 11 above into three classes (10%, 10-20% and $>20\%$) and run a multiple logistic regression model to determine the relationship between BP variability and CHD risk scores.

7.a. Will the data be used for non-CVD analysis in this manuscript? _____
Yes 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
 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.csc.unc.edu/ARIC/search.php>

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)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _____ Yes 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.csc.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.