

## ARIC Manuscript Proposal #3403

**PC Reviewed:** 6/18/19  
**SC Reviewed:** \_\_\_\_\_

**Status:** \_\_\_\_\_  
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**Priority:** 2  
**Priority:** \_\_\_\_\_

**1.a. Full Title:** The Utility of Biomarkers of Hypertensive End Organ Damage for Improving Cardiovascular Disease Risk Prediction Equations: Atherosclerosis Risk in Communities Study

**b. Abbreviated Title (Length 26 characters):** Biomarkers and Prediction of Cardiovascular Events

### 2. Writing Group:

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

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### **3. Timeline:**

The data needed for this analysis are currently available; we plan to submit for publication within 1 year.

### **4. Rationale:**

Current risk prediction equations for cardiovascular disease (CVD), including atherosclerotic CVD (ASCVD) and heart failure (HF) incorporate routinely available clinical variables.<sup>1-5</sup> Assuming adequate calibration and discrimination, the precision of the estimated risk is also dependent on accurate measurement of risk factors.

In particular, systolic blood pressure (SBP) is used in all established risk calculators as it is directly associated with CVD risk.<sup>6</sup> SBP measurement errors can be minimized by using a validated sphygmomanometer after a period of rest and averaging multiple blood pressure readings.<sup>7</sup> Notwithstanding measurement errors, SBP is also subject to diurnal, day-to-day, and month-to-month variability as a result of extrinsic factors related to posture, physical activity/exercise, diet, antihypertensive medication use, as well as intrinsic factors determined by the endocrine and nervous systems.<sup>8-13</sup> SBP variations have been shown to not only affect risk prediction of end organ damage from hypertension,<sup>14</sup> but also result in variability of CVD risk estimation,<sup>15</sup> which is used to guide preventive medication therapy.<sup>16-20</sup> In the ARIC study, estimated coronary heart disease/stroke risk in a given day varied based on different SBP readings and could classify a patient as high or low risk depending on the SBP value used.<sup>15</sup> Clearly this has clinical implications as decisions on preventative strategies in blood pressure management are predicated on the estimated 10-year CVD risk. Importantly risk prediction equations may perform less well in older adults as end organ damage becomes the major determinant of risk rather than risk factor levels.<sup>21</sup>

Several biomarkers have been shown to have value in CVD risk estimation.<sup>22</sup> These biomarkers are thought to reflect the cumulative exposure of the cardiovascular system to risk factors including SBP. Incorporating biomarkers that are associated with end organ injury/damage and hence likely to be reflective of the pathway that leads from elevated SBP to adverse events could be of value. Furthermore, as biomarkers have inherently less short-term variability compared to SBP, there may be discordance between the two, which warrants further study. Biomarkers of interest include high-sensitivity cardiac troponin T and I (cTnT), which has been shown to detect subclinical cardiac injury, and to predict incident ASCVD and HF in epidemiological cohort studies.<sup>23-25</sup> Other pertinent biomarkers include glomerular filtration rate (GFR), urine albuminuria, and carotid

intima-media thickness (cIMT), including plaque all of which are associated not only with long-term exposure to SBP but also with incident CVD.<sup>26</sup>

Therefore, in this study we evaluate the value of biomarkers of hypertensive end organ damage for CVD risk prediction. We hypothesize that these biomarkers are associated with cardiovascular outcomes and that they can improve CVD risk prediction, particularly among older adults. This may help guide the initiation and intensification of antihypertensive drugs.

## **5. Main Hypothesis/Study Questions:**

Aim 1: Study the association of biomarkers with cardiovascular outcomes stratified by SBP, estimated ASCVD risk, and age.

Hypothesis 1: Biomarkers are associated with incident ASCVD and HF irrespective of SBP and ASCVD but the association is stronger among older adults.

Aim 2: Compare the prognostic utility of biomarkers versus SBP for risk discrimination and reclassification of incident cardiovascular outcomes within different age strata.

Hypothesis 2: Biomarkers improve the discrimination and reclassification of incident ASCVD and HF compared to SBP. The performance of biomarkers is superior among older adults.

## **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).**

### Study Design and Inclusion/Exclusion criteria:

We will utilize data from ARIC visit 2 and follow up at visits 4 and 5 to evaluate differences in the prognostic utility of biomarkers with increasing age. Individuals with a) missing information on traditional risk factors including SBP, biomarkers of interest; b) prior history of ASCVD or HF in the respective analysis of incident outcomes; c) races other than white or black will be excluded.

### Exposure:

1. Following a rest period, three manual sitting BP measurements are made within a 10–15 min period, using a random zero sphygmomanometer. SBP is defined as the average of the 2<sup>nd</sup> and 3<sup>rd</sup> measurements.
2. CTnT concentrations are measured using a high-sensitivity assay, Elecsys Troponin T (Roche Diagnostics), on an automated Cobas e411 analyzer with a lower limit of measurement of 6 ng/L.<sup>23</sup>
3. GFR is estimated using the 2009 CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.<sup>27</sup>

4. Urine albuminuria is assessed as urinary albumin-creatinine ratio (UACR) from spot urine sample. Urine creatinine is measured by the modified kinetic Jaffé method. Urine albumin is measured by a nephelometric method either on the Dade Behring BN 100 or the Beckman Nephelometer.<sup>28</sup>
5. cIMT is measured using B-mode ultrasonography (Acuson 128 CT system) of the right and left carotid artery according to a standardized protocol by trained certified sonographers.<sup>29</sup>
6. Carotid plaque is defined if 2 of the following 3 criteria are met: abnormal wall thickness (defined as cIMT >1.5mm), abnormal shape (protrusion into the lumen, loss of alignment with adjacent arterial wall boundary), and abnormal wall texture (brighter echoes than adjacent boundaries).<sup>29</sup>

#### Outcomes:

1. ASCVD
  - a. **Incident** ASCVD includes the adjudicated outcomes of non-fatal myocardial infarction, non-fatal stroke, coronary heart disease or stroke mortality.
  - b. **Estimated** ASCVD risk is calculated using the 1) pooled cohort equations (PCE; includes age, sex, race, cigarette smoking, diabetes mellitus, SBP, antihypertensive medication use, total cholesterol, and high-density lipoprotein cholesterol (HDL-C));<sup>4</sup> and 2) ARIC Coronary Risk Score (ACRS; includes age, sex, smoking status, SBP, total cholesterol, HDL-C, hypertension medications use, and diabetes status).<sup>2</sup>
2. HF
  - a. **Adjudicated** incident HF is defined as the first HF hospitalization identified with International Classification of Diseases Code of 428 (Ninth Revision) or I50 (Tenth Revision) in any position on the hospital discharge list or a death certificate with death from HF in any position.<sup>30</sup>
  - b. **Estimated** HF risk is calculated using the ARIC Heart Failure Risk Score (HFRS; includes age, sex, smoking status, SBP, heart rate, body mass index (BMI), previous CHD, use of hypertension medications, and diabetes status).<sup>3</sup>

#### Covariates in multivariable models:

Age, sex, race/ethnicity, body mass index, heart rate, diabetes mellitus, hypertension status, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, antihypertensive medication use, lipid-lowering medication use, glucose-lowering medication use, body mass index, cigarette smoking.

#### Statistical Analysis:

Baseline characteristics will be tabulated by categories of SBP (<110 mm Hg, 110–129 mm Hg, 130–139 mm Hg, 140–159 mm Hg, ≥ 160 mm Hg). Continuous variables will be reported using mean (SD) or median (IQR) depending on normality of the data, while

categorical variables will be expressed as count (percentage). Differences will be tested using ANOVA, non-parametric testing, or chi-square testing as appropriate.

Biomarkers will be categorized as follows:

1. cTnT:  $\geq 13$  ng/L, 9–13 ng/L, 6–9 ng/L;  $< 6$  ng/L as reference. We will also examine continuous cTnT.
2. GFR:  $< 60$  ml/min/1.73 m<sup>2</sup>, 60–89 ml/min/1.73 m<sup>2</sup>;  $\geq 90$  ml/min/1.73 m<sup>2</sup> as reference
3. UACR:  $< 30$ , 30–299, and  $\geq 300$ ;  $< 30$  as reference.
4. IMT: 25–75<sup>th</sup> percentile,  $> 75^{\text{th}}$  percentile;  $< 25^{\text{th}}$  percentile as reference.
5. Carotid plaque: presence versus absence.

Aim 1: Incidence rates of cardiovascular outcomes will be calculated as number of events per 1000 person-years and stratified by SBP ( $< 110$  mm Hg, 110–129 mm Hg, 130–139 mm Hg, 140–159 mm Hg,  $\geq 160$  mm Hg). After testing and confirming the proportionality assumption, multivariable-adjusted Cox proportional hazards models will be used to study the association between biomarkers and incident ASCVD and HF stratifying by SBP.

Models will be sequentially adjusted for age, sex, race/ethnicity (Model 1), diabetes mellitus, hypertension status, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, use, lipid-lowering medication use, glucose-lowering medication use, body mass index, cigarette smoking. (Model 2).

We will also test for effect modification by creating multiplicative interaction terms between each biomarker and SBP ( $< 110$  mm Hg, 110–129 mm Hg, 130–139 mm Hg, 140–159 mm Hg,  $\geq 160$  mm Hg), age ( $< 65$  years, 65–75 years, and  $> 75$  years), and estimated ASCVD risk ( $< 7.5\%$  and  $\geq 7.5\%$ ) and testing for significance in the multivariable adjusted models as above.

Aim 2: Improvement in risk discrimination of incident ASCVD and HF will be calculated using area under receiving operating characteristic curves (AUC). The base model will include the PCE. Each biomarker will be added to the base model and improvement in AUC will be calculated. Criteria for selection of the biomarkers in final model include availability to primary care physicians, measurement reliability, and parsimony relative to the degree of improvement in the AUC.<sup>3</sup> We will compare performance of the base model (PCE *including* SBP) and the new model (biomarkers plus PCE *excluding* SBP) for predicting incident events using measures of calibration (goodness of fit) and discrimination (AUC). Improvement in reclassification will be assessed using net reclassification index (NRI) after addition of each biomarker to the base model.

We will perform these calculations in the overall study population and in age subgroups ( $< 65$  years, 65–75 years, and  $> 75$  years).

Limitations:

- The possibility of residual confounding cannot be excluded.
- Individuals with subclinical left ventricular dysfunction might be missed.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**

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?**

(This file ICTDER 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?**

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"?**

**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

**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)?**

1. High-Sensitivity Troponin T and Cardiovascular Events in Systolic Blood Pressure Categories: Atherosclerosis Risk in Communities Study
2. The impact of multiple single day blood pressure readings on cardiovascular risk estimation: The Atherosclerosis Risk in Communities study

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

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/>

**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.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

## References

- 1 Chambless LE, Heiss G, Shahar E, Earp MJ, Toole J. Prediction of ischemic stroke risk in the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 2004; **160**: 259–69.
- 2 Chambless LE, Folsom AR, Sharrett AR, *et al.* Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. *J Clin Epidemiol* 2003; **56**: 880–90.
- 3 Agarwal SK, Chambless LE, Ballantyne CM, *et al.* Prediction of incident heart failure in general practice: the Atherosclerosis Risk in Communities (ARIC) Study. *Circ Heart Fail* 2012; **5**: 422–9.
- 4 Goff DC, Lloyd-Jones DM, Bennett G, *et al.* 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **63**: 2935–59.
- 5 Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. *Am J Cardiol* 1976; **38**: 46–51.
- 6 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet (London, England)* 2002; **360**: 1903–13.
- 7 Ogedegbe G, Pickering T. Principles and techniques of blood pressure measurement. *Cardiol Clin* 2010; **28**: 571–86.
- 8 Parati G, Faini A, Valentini M. Blood pressure variability: its measurement and significance in hypertension. *Curr Hypertens Rep* 2006; **8**: 199–204.
- 9 Kohan DE, Rossi NF, Inscho EW, Pollock DM. Regulation of blood pressure and salt homeostasis by endothelin. *Physiol Rev* 2011; **91**: 1–77.
- 10 Fommei E, Iervasi G. The role of thyroid hormone in blood pressure homeostasis: evidence from short-term hypothyroidism in humans. *J Clin Endocrinol Metab* 2002; **87**: 1996–2000.
- 11 Manzoli L, Simonetti V, D’Errico MM, *et al.* (In)accuracy of blood pressure measurement in 14 Italian hospitals. *J Hypertens* 2012; **30**: 1955–60.
- 12 Franklin SS, Thijs L, Hansen TW, O’Brien E, Staessen JA. White-coat hypertension: new insights from recent studies. *Hypertens (Dallas, Tex 1979)* 2013; **62**: 982–7.
- 13 Mancina G, Parati G, Pomidossi G, Grassi G, Casadei R, Zanchetti A. Alerting reaction and rise in blood pressure during measurement by physician and nurse. *Hypertens (Dallas, Tex 1979)* 1987; **9**: 209–15.
- 14 Velasco A, Ayers C, Kaplan NM, *et al.* Optimal number of clinic BP measurements to predict 10-year risk of stroke and cardiovascular death in the Dallas Heart Study. *J Am Soc Hypertens* 2014; **8**: e3.
- 15 Ogunwale AN, Morrison AC, Sun W, *et al.* The impact of multiple single day

- blood pressure readings on cardiovascular risk estimation: The Atherosclerosis Risk in Communities study. *Eur J Prev Cardiol* 2016; **23**: 1529–36.
- 16 Martin SS, Sperling LS, Blaha MJ, *et al.* Clinician-patient risk discussion for atherosclerotic cardiovascular disease prevention: importance to implementation of the 2013 ACC/AHA Guidelines. *J Am Coll Cardiol* 2015; **65**: 1361–8.
  - 17 Stone NJ, Robinson J, Lichtenstein AH, *et al.* 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; published online Nov 7. DOI:10.1016/j.jacc.2013.11.002.
  - 18 Whelton PK, Carey RM, Aronow WS, *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. *Hypertension* 2017; published online Jan 1. <http://hyper.ahajournals.org/content/early/2017/11/10/HYP.000000000000065.abstract>.
  - 19 Arnett DK, Blumenthal RS, Albert MA, *et al.* 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. *Circulation* 2019; : CIR0000000000000678.
  - 20 Saeed A, Virani SS, Ballantyne CM, Taylor AA, Nambi V. Are All Benefits and Harms Equal? *J. Am. Coll. Cardiol.* 2018; **72**: 819–20.
  - 21 Saeed A, Nambi V, Sun W, *et al.* Short-Term Global Cardiovascular Disease Risk Prediction in Older Adults. *J Am Coll Cardiol* 2018; **71**: 2527–36.
  - 22 Yeboah J, McClelland RL, Polonsky TS, *et al.* Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA* 2012; **308**: 788–95.
  - 23 Saunders JT, Nambi V, de Lemos JA, *et al.* Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation* 2011; **123**: 1367–76.
  - 24 deFilippi CR, de Lemos JA, Christenson RH, *et al.* Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA* 2010; **304**: 2494–502.
  - 25 Folsom AR, Nambi V, Bell EJ, *et al.* Troponin T, N-terminal pro-B-type natriuretic peptide, and incidence of stroke: the atherosclerosis risk in communities study. *Stroke* 2013; **44**: 961–7.
  - 26 Hare DL, Toukhsati SR, Johansson P, *et al.* Depression and cardiovascular disease: a clinical review. *Eur Heart J* 2013; **162**: 1860–6.
  - 27 Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604–12.
  - 28 Ballew SH, Chen Y, Daya NR, *et al.* Frailty, Kidney Function, and Polypharmacy: The Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis* 2017;

**69**: 228–36.

- 29 Nambi V, Chambless L, Folsom AR, *et al.* Carotid Intima-Media Thickness and Presence or Absence of Plaque Improves Prediction of Coronary Heart Disease Risk. *J Am Coll Cardiol* 2010; **55**: 1600–7.
- 30 Rosamond WD, Chang PP, Baggett C, *et al.* Classification of heart failure in the atherosclerosis risk in communities (ARIC) study: a comparison of diagnostic criteria. *Circ Heart Fail* 2012; **5**: 152–9.