ARIC Manuscript Proposal #2709

PC Reviewed: 3/8/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Diastolic blood pressure, subclinical myocardial damage, and cardiac events: Implications for BP control in the post-SPRINT era.

b. Abbreviated Title (Length 26 characters): Diastolic BP and change in hs-cTnT

2. Writing Group:

Writing group members: John W. McEvoy; Yuan Chen; Andreea Rawlings; Christie M. Ballantyne; Roger S. Blumenthal; Josef Coresh; Elizabeth Selvin; others welcome

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

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3. Timeline: We aim to submit this paper for ARIC review <1 year from approval of the manuscript proposal

4. Rationale:

There have been several generations of increasingly sensitive troponin assays, which can detect troponin at concentrations that are substantially below the limits of detection of conventional assays in clinical practice (1, 2). Detectable levels of troponin by these high-sensitivity assays have been strongly predictive of future death, heart failure and fatal and non-fatal coronary heart disease (CHD) events in numerous rigorously conducted observational studies of asymptomatic persons including community-based populations (3-7).

The ability to detect subclinical myocardial damage using high sensitivity troponin assays is of heightened interest given results from the landmark Systolic Blood Pressure Intervention Trial (SPRINT) (8). The SPRINT trial reported significant improvements in CVD death and heart failure, with null results for myocardial infarction, among high risk non-diabetic hypertensive patients treated to a systolic BP target of less than 120 mm Hg. SPRINT will likely result in a paradigm shift of the definition and treatment of hypertension (9). However, SPRINT did not report on the impact of low systolic BP on CHD events such as unstable angina and revascularization. This has clinical implications because achieving a systolic BP of below 120 mm Hg will result in low diastolic BP (DBP), which can reduce coronary perfusion pressure and cause ischemia and myocardial damage among patients with coronary atherosclerosis. As such, high-sensitivity troponin may be of value in understanding whether a lower threshold of achieved BP, in particular low DBP, is associated with myocardial damage.

DBP is particularly important for CHD events because the coronary circulation is unique in that most blood flow occurs in diastole. During systole, the contracting LV myocardium compresses intramyocardial vessels and obstructs flow. Coronary perfusion pressure is the pressure gradient between the coronary arteries and the LV in diastole. In patients with coronary artery disease (CAD), a fall in DBP can lower perfusion pressure distal to a stenosis, thereby compromising myocardial perfusion, intensifying ischemia, and causing an increase in LV filling pressures, which can further reduce the perfusion gradient (10). Longstanding hypertension and LVH can also narrow the range of coronary arterial autoregulation**,** especially in the subendocardium. (11). Thus, in patients with LVH for example, subendocardial ischemia can occur with low DBP even in the absence of stenosis. Lindblad et al. demonstrated that lowering of DBP in 1,121 hypertensive men with hypertrophic ECGs increased the risk for MI (12).

While data for other outcomes vary, a J-curve has been repeatedly demonstrated for DBP and coronary events. In a study of 902 patients with moderate-to-severe hypertension, Cruickshank et al. found a strong J-curve relationship between death from MI and treated DBP in patients with CAD. The nadir of the J-curve in DBP was at 85 to 90 mm Hg, with an increase of mortality from MI on either side of this range (13). Farnett et al. confirmed this J-shaped relationship in their meta-analysis of a series of hypertension studies (14). In addition, the INVEST study enrolled 22,576 patients with CAD and hypertension and found that the primary outcome doubled when DBP was below 70 mm Hg and quadrupled when it was below 60 mm Hg. (15, 16)

Therefore, the aim of this analysis is to determine whether low DBP is associated with prevalent (as detected by abnormalities in high-sensitivity cardiac Troponin-T [hs-cTnT]) and progressive subclinical myocardial injury (as detected by trajectories of hs-cTnT change over follow-up). We will test this primary aim in the ARIC sample overall and in persons fulfilling SPRINT eligibility criteria, as well as among subgroups stratified by anti-hypertensive treatment status. We will also evaluate whether the combination of both low DBP and elevated baseline hs-cTnT (the latter as a surrogate for preceding structural heart disease [e.g. LVH] or subclinical macro/micro-vascular CAD] increases the risk for future adverse cardiac outcomes, inclusive of CHD, stroke, and death.

5. Main Hypothesis/Study Questions:

Aim 1a: To characterize the cross-sectional associations of DBP with high-sensitivity hs-cTnT.

Aim 1b: To characterize the prospective associations of baseline DBP with temporal changes in hs-cTnT (across ARIC visits 2, 4, and 5).

Aim 2: To evaluate whether elevated baseline hs-cTnT (visit 2) modifies the effect of reduced DBP on subsequent cardiac events, specifically fatal CHD and all-cause CHD (with secondary analyses for stroke and all-cause mortality).

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: Cross-sectional and longitudinal analyses of baseline DBP at visit 2 (1990-1992), baseline hs-cTnT, and hs-cTnT trajectories from visit 2, visit 4 (1996-1998), and visit 5 (2011-2013) [with competing events handled by IPAW techniques]. Prospective cohort analysis examining interaction between baseline DBP and hs-cTnT on the association with subsequent clinical events.

Hs-cTnT: Cardiac troponin T was measured at three time points in the ARIC Study using the same high sensitivity (pre-commercial) Roche assay.

> *Visit 2*: cardiac troponin T concentrations were measured from stored (visit 2) serum samples using a sandwich immunoassay method (Roche Diagnostics) implemented on a Roche Elecys 2010 Analyzer in 2012-2013 at the University of Minnesota as part of Dr. Selvin's ancillary study (#2009.16).
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> *Visit 4*: cardiac troponin T concentrations were measured from stored (visit 4) plasma samples using the same sandwich immunoassay method implemented on a Cobas e411 analyzer in 2010 at the Baylor College of Medicine as part of Dr. Ballantyne's ancillary study (#2008.10).

Visit 5- cardiac troponin T concentrations were measured from plasma samples using a sandwich immunoassay method implemented on a Cobas e411 analyzer at the Baylor College of Medicine.

Cardiovascular outcomes (Aim 2): This aim of the proposed study will focus on the interaction between low DBP and elevated hs-cTNT with incident CHD in particular, but also with stroke, and all-cause mortality. ARIC participants are contacted annually by telephone and reported hospitalizations and deaths are identified by report and active surveillance by surveying lists of discharges from local hospitals and death certificates from state vital statistics offices for potential events. Hospital records are abstracted and potential coronary heart disease and ischemic stroke are adjudicated by an end points committee.

Coronary heart disease: We will define incident coronary heart disease cases using the composite definition incorporating definite or probable myocardial infarction, cardiac procedures, and deaths from coronary heart disease identified during active surveillance for all hospitalizations and deaths among ARIC participants.

Stroke: Abstractors recorded stroke information if the list of discharge diagnoses included a cerebrovascular disease code (International Classification of Diseases, 9th Revision, code 430–437), if a cerebrovascular condition or procedure was mentioned in the discharge summary, or if a cerebrovascular finding was noted on a CT or magnetic resonance imaging report. Eligible cases were classified by computer algorithm and by a physician reviewer, according to criteria adapted from the National Survey of Stroke. Disagreements were adjudicated by another reviewer. Qualifying strokes were further classified into definite or probable hospitalized ischemic stroke (neuroimaging showed acute infarction or no hemorrhage) or hemorrhagic (intraparenchymal or subarachnoid) stroke on the basis of neuroimaging studies or autopsy, when available.

Mortality: Death from any cause identified during active surveillance of all participants in the ARIC study.

Sample:

Primary Sample. Of the 14 348 participants who attended visit 2, we will exclude participants who were neither white nor black and the small number of black persons in the Minnesota and Washington County cohorts, those with a history of prior CHD or Heart Failure, missing hscTNT at baseline, and those missing variables of interest.

Secondary Sample (SPRINT-eligible subsample)
- Non-diabetic persons over 50 years at visit 2 with SBP (both treated and untreated) >130 and<180 mmHg - AND either 10yr Framingham CVD Risk >=15% OR LVH on EKG OR ABI <0.9 OR GFR between 20-59

Exposure Variables

Categorical exposure: DBP <60, DBP 60-69, DBP 70-79, DBP 80-89 (**ref**), DBP 90-99, DBP >100 mmHg
Continuous exposure: DBP (modeled by restricted linear and cubic splines)

Primary analysis: baseline **visit 2** DBP exposure, modeled both categorically and continuously as above.
Covariates

Models will be adjusted for the following visit 2 variables: age (years), race-center (whites–Washington County, whites-Minneapolis, blacks-Jackson, blacks–Forsyth County, whites–Forsyth County), sex (male or female), body mass index (kg/m2), smoking (current, former, never), alcohol consumption (current, former, or never), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), estimated glomerular filtration rate ($mL*min^{-1}*1.73\ m^{-2}$), current lipid-lowering medication use (yes or no), blood pressure–lowering medication (yes/no), and history of diagnosed diabetes (yes/no).

Aim 1a - Statistical analyses: We will characterize the cross-sectional associations of DBP (assessed at visit 2) with hs-cTnT from visit 2 using linear regression models, with splines as necessary. We will also examine whether DBP is associated with categories of detectable hs-cTnT at visit 2 (binary variable >= 5ng/L) or elevated at visit 2 (>= 14ng/L) by logistic regression. We will consider the following core models:

> Model 1: age, sex, race-center.
> Model 2: age, sex, race-center, body mass index (kg/m2), smoking (current, former, never), alcohol consumption (current, former, or never), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), estimated glomerular filtration rate ($mL*min^{-1}*1.73\ m^{-2}$), current lipid-lowering medication use (yes or no), blood pressure–lowering medication (yes/no), and history of diagnosed diabetes (yes/no).
> Model 3: all variables in Model 2 + Visit 2 Systolic BP

We will also test for interactions by age, sex, and race.

Aim 1b – Statistical analyses:

The outcome for this aim is temporal change in hs-cTnT measured at visits 2, 4, and 5. For individuals with values <3 we will impute a value between 0 and 3 based on a normal distribution. We will use regression models to estimate associations between DBP categories and mean troponin change (trajectory) over time and fit models using generalized estimating equations to account for the within person correlations of troponin arising from the analysis of repeated measures over time. We will use unstructured correlation matrices and robust variance estimates. Time since baseline may need to be modeled using a linear spline. This potential spline term, if needed, would allow for a

nonlinear association between time and hs-cTnT change and could more appropriately fit the study design if it is supported by diagnostic Lowess smoothers. The primary coefficients of interest were the interactions between baseline DBP and the time spline terms, which address the hypothesis of differences in temporal hscTNT change by DBP category after adjustment for covariates.

We will test for linear trend across categories of DBP level by using variables assigned a value of 1 through 6 for each category.

We will also use an inverse probability of attrition weighting (IPAW) approach to account for potential informative missingness of hs-cTnT at follow-up visits (due to competing deaths for example). PROC GENMOD will be used for the generalized linear models, with a REPEATED statement to account for correlations between observations and a WEIGHT statement to incorporate the inverse probability weights.

We will consider the following core models:

Model 1: age, sex, race-center.
Model 2: age, sex, race-center, body mass index (kg/m2), smoking (current, former, never), alcohol consumption (current, former, or never), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), estimated glomerular filtration rate ($mL*min^{-1}*1.73\ m^{-2}$), current lipid-lowering medication use (yes or no), blood pressure–lowering medication (yes/no), and history of diagnosed diabetes (yes/no).
Model 3: all variables in Model 2 + Visit 2 Systolic BP

We will conduct this analysis in the sample overall, as well as after stratification by visit 2 hs-cTnT level (<5, 5-13, >14 ng/L)

<u>Aim 2 – Statistical analyses</u>

We will generate a Kaplan-Meier plot to visually show the survival functions for the different outcomes by categories of DBP. We will estimate hazard ratios and their 95% confidence intervals using Cox proportional hazards models with adjustment for covariates. The proportional hazards assumption will be examined using log-(-log) plots and by testing risk factor-by-time interactions; if the assumption is violated the interactions term(s) will be kept in the model and the time-dependent nature of the risk will be interpreted accordingly. We will consider the following core models:

Model 1: age, sex, race-center.
Model 2: age, sex, race-center, body mass index (kg/m2), smoking (current, former, never), alcohol consumption (current, former, or never), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), estimated glomerular filtration rate ($mL*min^{-1}*1.73\ m^{-2}$), current lipid-

lowering medication use (yes or no), blood pressure–lowering medication (yes/no), and history of diagnosed diabetes (yes/no).
Model 3: all variables in Model 2 + Visit 2 Systolic BP

We will conduct this analysis in the sample overall, as well as after stratification by visit 2 hs-cTnT level (<5, 5-13, >14 ng/L) and by stratification by hypertension medication treatment status (yes, no, [excluding HTN treatment yes/no in the regression model]). To characterize the continuous associations, we will generate piece-wise linear splines with knots corresponding to the cutoffs for the DBP categories and we will also implement restricted cubic splines to obtain a smoother fit to the data.

We will formally test for interactions by race and sex, and present stratified analyses if there is evidence for interaction.

Sensitivity analyses:

Sensitivity Analysis: New exposure model with DBP as time-varying exposure by updating values at visits 2 and 3, modeled as above, for the outcomes in aims 1b and 2.

Sensitivity Analysis: New exposure model with baseline visit 2 DBP in the **SPRINT subsample** only, modeled both categorically and continuously as above (excluding history of DM yes/no in the model).

Sensitivity Analysis: New exposure model with baseline visit 2 DBP in a **subsample** of persons **on HTN treatment who have SBP <=130 at baseline**, DBP will be modeled by categories of <60, 60-70, 70-80, >80 mmHg (will need to put in achieved SBP within each of the DBP categories in the table for this)

Limitations:

- Observational study may be associated with residual confounding
- We may lack power for some of the categories of DBP
- IPAW approach may not fully account for bias resulting from attrition

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 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?

____ 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)? None

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal

_X__ A. primarily the result of an ancillary study (list number* 2009.16 and 2008.10)

___ 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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