ARIC Manuscript Proposal # 1846

PC Reviewed: 9/13/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Subclinical cardiac damage explains the changing association between blood pressure and coronary heart disease events with age.

b. Abbreviated Title (Length 26 characters):
hs-cTNT and CHD events

2. Writing Group:
Writing group members:
Seamus Whelton, Kunihiro Matsushita, Ron Hoogeveen, Christie Ballantyne, Vijay Nambi, Josef Coresh, Others welcome.

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

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3. Timeline:
Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next six months.

4. Rationale:

Hypertension is a well-established risk factor for cardiovascular disease and is the most important risk factor in the elderly population[1]. There is a linear relationship between advancing age and increasing systolic blood pressure (SBP). Conversely, diastolic blood pressure (DBP) slowly increases until approximately age 55, after which it plateaus and then gradually declines[2].

Elevated DBP is a superior predictor of CHD compared to SBP in those less than 50 years of age. However, as age increases the strength of DBP to predict CHD diminishes and it is no longer a significant risk factor after the age of 60[3]. In fact, an inverse relationship between DBP and CHD has been demonstrated in people over the age 60[4]. Therefore, in the elderly population for any given SBP a lower DBP may be associated with an increased risk of CHD. This age dependent relationship between DBP and CHD has been characterized as a j-curve[5,6,7].

The coronary arteries are perfused during diastole and the reduction of DBP beyond a certain lower physiologic threshold can lead to under perfusion and myocardial ischemia. A number of mechanisms to explain why the elderly population is susceptible to decreased DBP have been proposed including: 1) a hardening of the large arteries with aging, 2) underlying poor health or chronic illness, and 3) overaggressive anti-hypertensive treatment[5].

Cardiac troponin is significantly associated with adverse cardiovascular outcomes in patients with known cardiac disease in the general population[8]. However, using traditional assays less than one percent of the population has detectable levels of cardiac troponin. A new high sensitivity cardiac troponin (hs-cTNT) assay is now available with a sensitivity increase of approximately ten times over the previous assay[9]. This allows for a marked increase in the detection of hs-cTNT in a population without symptomatic cardiovascular disease.

A recent publication demonstrated that an elevated hs-cTNT level is significantly associated with CHD and may be a superior predictor of CHD risk compared to other novel serum markers such as hs-CRP[9]. The increased risk of CHD associated with hs-cTNT is likely mediated through non-atherthrombotic mechanisms which are not yet fully understood, but may include asymptomatic ischemia or coronary microvascular dysfunction[9].

The absence of an association between elevated DBP and increased risk of CHD in the elderly may be due to a number of mechanisms, which have been previously described. hs-cTNT represents a novel serum biomarker that may identify a subgroup of elderly patients with an increased risk of CHD in whom an elevated DBP is not a predictive marker. Additionally, an association between elevated hs-cTNT and low DBP would also support sub-clinical ischemia as an underlying mechanism for the j-curve relationship.

5. Main Hypothesis/Study Questions:

Measurement of hs-cTNT in an elderly population may identify a subgroup at particular risk for CHD in whom low DBP is associated with higher risk and elevated DBP is not predictive of CHD.

Among individuals without detectable hs-cTNT the association between DBP and CHD will remain linear and similar in younger and older individuals.

Measurement of NT-Pro-BNP may be needed to fully characterize the subgroup of elderly individual with intacts hearts in which the DBP and CHD relationship is unaltered at older age (e.g. no elevations in NT-pro-BNP or hs-TnT).

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).

Data:

Inclusion criteria:

- Participants in whom a serum hs-cTNT was measured at Visit 4 (n~11,000).

Exclusion criteria:

- Participants with known coronary artery disease (history, EKG evidence of angina or myocardial infarction), participants without a recorded hs-cTNT measurement. We will compare included and excluded individuals and in sensitivity analyses also examine the primary hypothesis in the subgroup with existing disease where troponin elevations are common and the J-shape may be more accentuated.

Exposure Variables:

-DBP. SBP will be examined in secondary analyses and blood pressure lowering medications will be considered.
- hs-cTNT. NT-pro-BNP will also be examined as a second variable indicating cardiac dysfunction.

Confounding/Interacting Variables:

-Age, sex, race, cholesterol levels (total, LDL, HDL), systolic blood pressure, hypertension, body mass index (height, weight), glomerular filtration rate, cystatin C, smoking (current, former, never), diabetes, hs-CRP, alcohol consumption, carotid intimal medial thickness

Outcome Variables:

- Primary: Coronary heart disease (non-fatal myocardial infarction, fatal myocardial infarction, sudden cardiac death). Heart failure and death will be examined in secondary analyses.

Analysis plan and methods:

- Analyses will be stratified by age <60 years old and ≥ 60 years old. Within each of these age ranges we will separate participants into low, moderate, and high DBP groups. Continuous variables will be compared using one-way ANOVA testing and categorical variables will be compared using either chi-squared or Fisher's exact test. Hazard ratios and associated confidence intervals will be calculated for the primary endpoint separated by age range and DBP group. Additional models adjusting for established CHD risk factors will be performed.
The primary hypothesis will also be examined modeling DBP as a continuous variable testing the significance of deviations from linearity using a spline with knots at 70 and 80 mmHg. We hypothesize that among older participants (age>60 years), at least one of these knots will be statistically significant and the association will be J-shaped. However, when limited to individuals without hs-TnT elevations, the knot will no longer be significant.

Blood pressure medications will be important to consider. There is not perfect way to model the effect of medications since they are prescribed based on blood pressure levels and sometimes physicians perceptions of CVD risk. We will first conduct analyses stratified by use of antihypertensives (none vs. some; none, one agent, two or more medications). If associations are similar we will adjust for use of antihypertensives. We will also examine if the type of antihypertensive used interacts with the same of the DBP and CHD association.

We will also examine the primary hypothesis for SBP.

We will conduct similar analyses for NT-Pro-BNP as another marker of cardiac dysfunction. Although the physiology is different, it may be useful to combine NT-Pro-BNP and hs-TnT to identify the subgroup of individuals with intact hearts at older age, e.g. low levels on both markers. It may be that only older individuals without elevations of either markers have a similar DBP to CHD relationship as younger individuals.

We will examine whether stratifying by hsTnT will allow for better risk modeling of the BP (SBP, DBP and medication) with CHD and improve on the current risk prediction strategy. It is possible, that even if hsTnT improves our understanding of the DBP to CHD risk relationship it may not add sufficient information to improve overall risk prediction. Even if overall risk prediction isn't improve this analysis might provide insight into how blood pressure should be interpreted among older individuals with elevated hs-TnT.

Summary/conclusion:
- Analysis of the relationship between DBP and hs-cTNT in an elderly population may provide an improved risk prediction model for CHD events. Additionally, if an association between BP and incident CHD in elderly patients is altered in the presence of increased hs-cTNT it would strengthen the argument for sub-clinical ischemia and cardiac dysfunction as influencing the blood pressure trajectory and its consequences in older adults.

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

1. **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)?

MP1517: Inflammation clarifies age related changes in the relationship of serum cholesterol to risk of coronary heart disease: The Atherosclerosis Risk in Communities Study

MP1563: Novel highly sensitive cardiac Troponin-T (hs-cTnT) assay, mortality, and major
adverse cardiovascular events in the ARIC Study

MP1564: Correlation of High Sensitivity Troponin-T (hs-cTnT) and Amino Terminal proBrain Natriuretic Peptide (NT-proBNP) with Renal Function Parameters; and Association with
Mortality and Adverse Cardiovascular Event

MP1808: The utility high sensitivity cardiac troponin t in the prediction of heart failure risk

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

_X__ A. primarily the result of an ancillary study (list number* __troponin ancillary_____)

___ 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.

1. ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly J Am Soc Hypertens. 2011 Jul-Aug;5(4):259-352.

2. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, andTreatment of High Blood Pressure. Chobanian AV, et al. Hypertension. 2003 Dec;42(6):1206-52.

3. Systolic versus diastolic blood pressure and risk of coronary heart disease. The Framingham study. Kannel WB et al. Am J Cardiol. (1971) Apr;27(4):335-46.

4. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study.Franklin SS et al. Circulation. (2001) Mar 6;103(9):1245-9.

5. The J-curve between blood pressure and coronary artery disease or essential hypertension: exactly how essential? Messerli FH et al. J Am Coll Cardiol. (2009) Nov 10;54(20):1827-34.

6. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial.2003 Dec 3; 290(21) :2805-16.

7. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. et al. JAMA. (1991) Jun 26;265(24):3255-64.

8. The prognostic value of troponin in patients with non-ST elevation acute coronary syndromes: a meta-analysis. Heidenreich PA et al, J Am Coll Cardiol. 2001 Aug;38(2):478-85.

9. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Saunders JT et al. Circulation. (2011) Apr 5;123(13):1367-76.