

ARIC Manuscript Proposal #1917

PC Reviewed: 3/20/12
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Association of diastolic dysfunction with high sensitivity troponin T and NT-proBNP across left ventricular geometries in the community – A preliminary analysis from the ARIC study

b. Abbreviated Title (Length 26 characters):

Diastolic dysfunction and high sensitivity troponin T in ARIC

2. Writing Group:

Writing group members: Amil M Shah, Christie Ballantyne, Dalane Kitzman, Ervin Fox, Ken Butler, Kunihiro Matsushita, Suma Konety, Scott D. Solomon; Others welcome.

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:

Analysis will begin once this manuscript proposal is approved and approximately 3,000 Visit 5 echocardiograms have been performed and fully analyzed (anticipate June 2012). Anticipate manuscript completion in approximately the following 3 months.

4. Rationale:

With the advent of highly sensitive assays, circulating troponin T is detectable in a sizeable proportion of asymptomatic community dwelling individuals, with the prevalence and magnitude of detectable troponin significantly higher with older age, black race, and cardiovascular comorbidities such as hypertension, diabetes, and renal insufficiency.^{1,2} Among elderly cohorts in particular, troponin T is detectable in approximately 66% of individuals using these novel assays.^{1,3} Interestingly, the association between this biomarker and clinical events may be stronger with incident heart failure as opposed to incident ischemic events.^{3,4} Detectable troponin levels with these highly sensitive assays demonstrate a significant and graded association with cardiovascular mortality and incident heart failure, even after adjustment for relevant clinical characteristics and comorbidities.^{1,2,3}

The mechanisms mediating this association are unclear. Troponin elevation is significantly associated with increased left ventricular mass and wall thickness and reduced LVEF by MRI² and with the presence of electrocardiographic left ventricular hypertrophy.¹ Together, these findings suggest alterations in cardiac structure and function associated with cardiovascular comorbidities may partially mediate or occur in tandem with biomarker elevation. Diastolic dysfunction shares many risk factors with LV concentric remodeling, can occur in the absence of overt ventricular remodeling,⁵ and is associated with mortality and incident heart failure in the elderly.^{6,7,8} While strong associations with LV structure and gross systolic function (measured by LVEF) have been described, the relationship between troponin levels detected with high sensitivity assays and measures of diastolic dysfunction has not been well described. Among 1005 community dwelling individuals greater than 70 years old, troponin I levels measured with a standard assay were detectable with 22% of participants and significantly correlated with LV mass and LVEF but not diastolic function.⁹ However, this analysis was significantly limited by both the relatively small proportion of participants with detectable troponin and the relatively crude assessment of diastolic function, based solely on mitral inflow Doppler parameters.

5. Main Hypothesis/Study Questions:

We hypothesize that, among asymptomatic ARIC participants with LVEF>50%, echocardiographic parameters of diastolic dysfunction will be associated with higher levels of troponin T using the high sensitivity assay, independent of LV mass index and LV wall thickness.

Specifically, we aim to determine the association of parameters of diastolic dysfunction (tissue Doppler imaging [TDI] E' – a measure of early diastolic relaxation; E wave/E' ratio – a measure of instantaneous LV filling pressure; and left atrial volume index [LAVi] – a marker of chronic elevations in LV filling pressure) with presence and magnitude of hsTnT overall and stratified by LV geometry, by LVEF, and by prevalent heart failure.

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:

This will be a cross-sectional analysis of the first 3,000 ARIC Visit 5 echocardiograms analyzed.

Inclusion/exclusion criteria:

Participants in atrial fibrillation or with missing data for key echocardiographic criteria (E wave, A wave, E wave deceleration time, TDI E', and LAVi) or biomarkers (hsTnT or NT-proBNP) will be excluded from this analysis.

Key variables of interest:

1. Echocardiographic variables (visit 5 echo) of LV diastolic function (E wave, A wave, E wave deceleration time, TDI E', and LAVi), LV structure (wall thickness, relative wall thickness, systolic and diastolic diameters and volumes), LV systolic function (LVEF, TDI S', LV end-systolic elastance), and pulmonary artery systolic pressure
2. Laboratory values (visit 5): high sensitivity troponin T, NT-proBNP, serum albumin and creatinine, urine albumin and creatinine, hemoglobin and hematocrit, glucose, hemoglobin A1C, total cholesterol, triglycerides, HDL, LDL
3. Clinical covariates (visit 5): age, gender, race/ethnicity, height, weight, blood pressure, heart rate, history of hypertension, diabetes, dyslipidemia, coronary artery disease, prior MI or revascularization procedure, prior stroke or TIA, peripheral arterial disease, heart failure, prior hospitalization for heart failure

Data analysis:

Troponin T will be modeled as both an ordered categorical and a continuous variable. For the categorical analysis, the study population will be divided into groups based on visit 5 hsTnT levels: participants with undetectable level will be placed in one group and the other 4 groups will be generated by splitting the observed hsTnT levels into approximate fourths. Clinical covariates, laboratory variables, echocardiographic parameters of structure and function, and echocardiographic parameters of diastolic function (E', E wave/E', LAVi, E/A ratio, E wave deceleration time) will be described by hsTnT category. For the continuous analysis, hsTnT levels will be log transformed, with undetectable values assigned a value just below the lower detection limit of the assay (0.0029 µg/L). Correlation of hsTnT level with echocardiographic parameters of LV structure, systolic function, and diastolic function will be assessed by univariable linear regression and by multivariable linear regression after adjusting for age, gender, race, blood pressure at time of echo, history of hypertension, diabetes, coronary artery disease, eGFR, and NT-proBNP. A second multivariable model will then be generated which further adjusts for LV mass index, LV relative wall thickness, and LVEF. Additional models with interaction terms for gender and race will be generated to assess for effect modification of the relationship between diastolic parameters and hsTnT levels by race or gender. Finally, participants will be divided into categories of diastolic dysfunction (normal, mild, moderate, severe) based on a modification of the Redfield criteria which

Anticipated methodologic limitations:

An additional limitation of this analysis is its cross-sectional nature. We anticipate performing a follow-up analysis to assess the relationship between diastolic function, hsTnT, and incident HF (both HF with preserved LVEF and HF with reduced LVEF) once adequate clinical follow-up post-Visit 5 is available.

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

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.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)?

MS#1811- (Oluleye et al) Association of high sensitive Troponin T (hs-cTnT), N-Terminal pro- brain natriuretic peptide (NT-proBNP) and high sensitivity C- reactive protein (hs-CRP) with cause- specific mortality: ARIC study

MS#1808- (Nambi et al) The utility high sensitivity cardiac troponin t in the prediction of heart failure risk

MS#1757 (Nambi et al) The association of high sensitivity troponin with heart failure, mortality and recurrent coronary heart disease (CHD) in individuals with prevalent CHD

MS#1564 (Saunders et al) Correlation of High Sensitivity Troponin-T (hs-cTnT) and Amino Terminal pro-Brain Natriuretic Peptide (NT-proBNP) with Renal Function Parameters; and Association with Mortality and Adverse Cardiovascular Events

MS#1172 (Nambi et al) Lp-PLA2 and hs-CRP as Predictors of Ischemic Stroke

MS#940 (Ballantyne et al) Lipoprotein-associated phospholipase A2, high sensitivity c-reactive protein, and risk for ischemic stroke

MS#934 (Folsom et al) An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers

MS#889 (Ballantyne et al) Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein and risk for incident coronary heart disease in middle-aged men and women in Atherosclerosis Risk in Communities Study

MS#606 (Folsom et al) C-reactive protein and incident coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study

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.

References

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- ⁴ Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, Tjora S, Domanski MJ, Gersh BJ, Rouleau JL, Pfeffer MA, Braunwald E. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med* 2009;361:2538-47.
- ⁵ Solomon SD, Janardhanan R, Verma A, Bourgoun M, Daley WL, Purkayastha D, Lacourciere Y, Hippler SE, Fields H, Naqvi TZ, Mulvagh SL, Arnold JMO, Thomas JD, Zile MR, Aurigemma GP. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomized trial. *Lancet* 2007;369:2079-87.
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- ⁹ Eggers KM, Lind L, Ahlstrom H, Bjerner T, Barbier CE, Larsson A, Venge P, Lindahl B. Prevalence and pathophysiological mechanisms of elevated cardiac troponin I levels in a population-based sample of elderly subjects. *Eur Heart J* 2008;29:2252-8.
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