

ARIC Manuscript Proposal #2982

PC Reviewed: 5/9/2016

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Priority: 2

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Status: _____

Priority: _____

1.a. Full Title:

Association and Prediction of Incident Cardiovascular Events by Cardiac Biomarkers in Older Adults: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):

Cardiac Biomarkers And Global CVD

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3. Timeline:

Analysis to start immediately; Manuscript to be written and sent for publication within one year of approval.

4. Rationale:

Cardiovascular disease (CVD) accounts for nearly 801,000 deaths in the USA. About 2,200 Americans die from CVD related causes each day, an average of 1 death every 40

seconds¹. About 92.1 million American adults are living with some form of CVD including coronary heart disease (CHD) or heart failure (HF) or the after-effects of stroke.

Atherosclerotic CVD risk prediction is currently performed using the pooled cohort (PCE) equation. However, most adults aged ≥ 65 years exceed the 7.5% risk threshold despite optimal risk factor profile.² Indeed, white men aged 63–75 years, white women aged 71–75 years, black men aged 66–75 years, and black women aged 70–75 years would be recommended for statin treatment for primary prevention even with optimal risk factors (e.g., total cholesterol 170 mg/dL, HDL-C 50 mg/dL, SBP 110 mm Hg without BP meds, no diabetes, and no smoking).² In addition, the risk equation cannot be used for individuals who are already on statin therapy or for prediction of recurrent CVD events. The PCE is also limited by not accounting for risk for HF, which is the most common CVD event in the elderly and a major cause of medical expenditures.

Data from the NHLBI-sponsored Chicago Heart Association Detection Project in Industry, Atherosclerosis Risk in Communities (ARIC), and Cardiovascular Health Study (CHS) cohorts indicates that HF incidence approaches 21 per 1000 population after 65 years of age¹. HF incidence rates in males approximately double with each 10-year age increase from 65 to 85 years; however, the HF incidence rate triples for females between ages 65 to 74 and 75 to 84 years. (Incidence and Prevalence: 2006 Chart Book on Cardiovascular and Lung Diseases. Bethesda, MD: National Heart, Lung, and Blood Institute; 2006.)

Given the poor prognosis in persons with overt HF, HF prevention is a medical priority, particularly for HF with preserved ejection fraction (HFpEF), which currently does not have any proven therapy and is predominantly managed symptomatically. Furthermore, identifying patients who are at higher risk for recurrent HF is pragmatic for ensuring appropriate prevention therapies and strategies. The AHA/ACC Risk Assessment Work Group has “examined the possibility of including HF as an outcome. However, study-by-study ascertainment and adjudication of HF varied considerably, and therefore HF could not be included as an outcome”³. In this context, since 2005, the ARIC Study has been adjudicating all HF hospitalization cases by physician reviewers using medical records to ensure that the leading cause of cardiovascular morbidity in the older adults can be accounted for accurately.

A high-sensitivity troponin T (hs-cTnT) assay, which was recently approved in the United States for clinical use in detection of acute coronary syndromes (ACS), can identify concentrations that are 10-fold lower than widely used fourth-generation assays. The limit of detection for hs-cTnT is 5 ng/L (limit of blank is 3ng/L), the 99th percentile of the hs-cTnT distribution is 14 ng/L in the general population and a high percentage of asymptomatic individuals should have a detectable value a high hs-cTnT.

In prior studies, addition of both hs-cTnT and NT-proBNP improved risk prediction for incident CHD and HF beyond traditional risk factors used in the ARIC risk equations for CHD and HF.^{4,5} Similarly, hs-cTnT has also shown to improve risk prediction for HF hospitalization compared with clinical variables and also reported that a laboratory-based model using only age, sex, race, hs-cTnT, and NT-proBNP performed as well as the ARIC HF model with clinical variables.⁵ Recently, it was shown in the ARIC study that temporal increases in hs-cTnT, suggestive of progressive myocardial damage, are independently associated with incident CHD, death, as well as HF in primary prevention population⁶. Further, serial determination of hs-cTnT changes added clinically pertinent information to baseline testing⁶. This study suggested the usefulness of hs-cTnT levels in prognostic assessments and targeting prevention strategies to high-risk individuals, especially persons at high risk for HF.

In a study by Koenig et al., secondary CVD events were assessed in patients with stable CHD over an 8-year follow up⁷. In the multivariate analysis, hs-cTnT was associated with a hazard ratio for of 2.83 (95% CI, 1.68–4.79) for secondary events. Further adjustment for cystatin C, NT-proBNP, and C-reactive protein reduced this association slightly (HR, 2.27; 95% CI, 1.31–3.95); P for trend 0.002). However, the mean age in this study population was 58 years and HF events were not included in the outcomes.

The improvement in risk prediction of HF in older adults by incorporating change in hs-cTnT has been demonstrated in the CHS cohort⁸.

High sensitivity C-reactive protein (hs-CRP) has also been approved for risk assessment.

However, at ARIC visit 4, cholesterol level in individuals aged <65 years was strongly associated with CHD risk, whereas in individuals aged 65–74 years, the relation was attenuated and LDL-C was no longer significantly associated with CHD.⁹ In older individuals with elevated hs-CRP

levels, cholesterol level was significantly less predictive of CHD ($p < 0.05$), whereas in those with hs-CRP level < 2 mg/L, there was no significant difference compared with younger individuals⁹.

There has been limited evidence of using these biomarkers for incidence of CVD events or the recurrence of CVD events, including HF, in older adults (cohort in visit 5 of the ARIC study mean age=75 years). Nor has hs-cTnT been used in conjunction with NT-pro-BNP, hs-CRP and lipid markers in risk prediction for CVD events in this age group.

We, therefore, aim to assess the association of hs-cTnT with a short term risk for incident global CVD events after ARIC visit 5. Further, we also aim to assess the utility of using these novel biomarkers to predict recurrent CVD events in patients with established HF, stroke and CHD at visit 5.

5. Main Hypothesis/Study Questions:

Primary: We hypothesize that cardiac biomarkers (hs-cTnT, NT-pro-BNP) and inflammatory marker (hsCRP) will predict risk for incident heart failure, coronary heart disease, stroke and global cardiovascular events (CHD, stroke and HF) in older adults in a manner that has previously been shown in ARIC study in a relatively younger age group.

Secondary: We also hypothesize that the pooled cohort risk equation underestimates the risk of global cardiovascular disease events in the older adults.

In addition, the combination of cardiac biomarkers (hs-cTnT, NT-ProBNP) and inflammatory marker (hsCRP) in addition to the traditional risk factors improve risk prediction of global CV events in older individuals compared to the PCE alone.

Tertiary: We will also assess the change of cardiac biomarkers between visit 4 and visit 5 (a total of approximately 15-year time period) in additional exploratory analyses.

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 from ARIC visit 5 (2011-2013) will be used. These values will serve as the exposure variable and incident CHD, ischemic stroke and HF will be the outcomes. Follow up will be upto Demcember 31st 2014.

Endpoints to be assessed:

1. Total/All CHD (fatal CHD, definite/probable MI, cardiovascular revascularization)
2. Hard CHD ((fatal CHD, definite/probable MI)
3. Stroke (ischemic/ thrombotic stroke)
4. HF hospitalization consists of definite and probable acute decompensated HF (as adjudicated in the ARIC study)
5. Global CVD (CHD + stroke+ heart failure)
6. CV mortality and total mortality

Covariates will include age, gender, race, heart rate, body mass index (BMI), lipids, current smoking, diabetes, hypertension, systolic blood pressure, eGFR, prediabetes (HbA1c 5.7- ≤6.6%), impaired fasting glucose (fasting glucose>100mg/dl), hs-CRP, hs-cTnT, NT-proBNP.

Inclusion/ exclusion criteria:

All eligible ARIC participants will be included in the study.

Standard ARIC exclusions (race exclusions for different communities) will apply. The major exclusion criteria include participants without data on exposure, outcome, or covariates.

Analysis:

Participant characteristics and cardiac biomarkers will be reported as means and standard deviations, as medians and inter-quartile ranges (IQR), or as frequencies and percent, where appropriate. If lack of normality is not a concern and transformation is not required, then conventional statistics will be used. For non-normal data, transformations and/ or non-parametric testing will be used.

HF hazard ratios across hs-cTnT and NT-pro-BNP categories will be calculated using Cox-proportional hazards models. The proportionality assumption of all Cox models will be assessed by inspecting the log (-log [survival function]) curves.

Regression models will be first adjusted for age, sex and race. Secondary models will be adjusted for;

- Additional variables used in the PCE i.e. total and high-density lipoprotein cholesterol levels, systolic blood pressure, use of antihypertensive medications, smoking status, diabetes mellitus status (defined as fasting blood glucose ≥ 126 mg/dL or use of diabetic medications).
- Variables used in the ARIC HF model (model 1 plus SBP, BP meds, current smoking, diabetes, BMI, heart rate and for covariates (the variables for the pooled cohort risk equation)).
- Variables of the PCE as well as NT-pro-BNP and hs-CRP

We will create 4–8 models, with a few parsimonious models with clinically readily available predictors and a few more complex models with nontraditional predictors such as NT-pro-BNP, hs-cTnT and hs-CRP.¹⁰ Competing risk of death will be analytically taken into account with Fine–Gray proportional sub distribution hazards models. Each of these models will be contrasted for calibration chi-square, C statistic, net reclassification improvement (NRI), and integrated discrimination improvement (IDI).^{11,12}

Based on prediction improvement and availability in clinical practice, we will select 2 prediction models: a parsimonious model with best performance readily applicable to current clinical practice and a more complex model.

Follow up time will begin at entry into visit 5 until December 31st, 2014.

Methodological limitations/ challenges:

Biomarker (hs-cTnT, hs-CRP, NT-pro-BNP) measurements will be on frozen samples. Measurements of each biomarker will be taken at one point in time.

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.csc.unc.edu/ARIC/search.php>

_____ Yes _____ No

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)?

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.

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:

- PI: Christie M. Ballantyne, MD

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 shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript _____ Yes No.

References:

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4. 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.
5. Nambi V, Liu X, Chambless LE, et al. Troponin T and N-terminal pro-B-type natriuretic peptide: a biomarker approach to predict heart failure risk--the Atherosclerosis Risk in Communities study. *Clinical chemistry* 2013;59:1802-10.
6. McEvoy JW, Chen Y, Ndumele CE, et al. Six-year change in high-sensitivity cardiac troponin t and risk of subsequent coronary heart disease, heart failure, and death. *JAMA Cardiology* 2016;1:519-28.
7. Koenig W, Breitling LP, Hahmann H, Wusten B, Brenner H, Rothenbacher D. Cardiac troponin T measured by a high-sensitivity assay predicts recurrent cardiovascular events in stable coronary heart disease patients with 8-year follow-up. *Clinical chemistry* 2012;58:1215-24.
8. deFilippi C, Wasserman S, Rosanio S, et al. Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. *JAMA* 2003;290:353-9.
9. Whelton SP, Roy P, Astor BC, et al. Elevated high-sensitivity C-reactive protein as a risk marker of the attenuated relationship between serum cholesterol and cardiovascular events at older age: the ARIC Study. *American journal of epidemiology* 2013;178:1076-84.
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12. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;27:157-72; discussion 207-12.