ARIC Manuscript Proposal #3507

PC Reviewed: 11/12/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: High-sensitivity cardiac troponin I for mortality and cardiovascular risk stratification in older adults.

b. Abbreviated Title (Length 26 characters): Hs-cTnI in older adults

2. Writing Group:

Writing group members: Olive Tang; Kunihiro Matsushita; Josef Coresh; Ron Hoogeveen; B. Gwen Windham; Christie Ballantyne; Elizabeth Selvin; others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___OT__ **[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:

All measurements required for this proposal have been collected. We aim to complete the manuscript <1 year from the time of approval and release of the data.

4. Rationale:

Compared to traditional cardiovascular risk factors measured in mid-life, risk factors measured in late life risk tend to be less strongly associated with subsequent cardiovascular and

mortality risk. In older age, objective biomarkers reflecting summative cardiomyocyte damage, such as high-sensitivity cardiac troponin I (hs-cTnI), could help improve risk assessment. High-sensitivity assays detect minute elevations in cardiac troponin I (cTnI), well below those used for diagnosis of acute myocardial infarctions. The Abbott hs-cTnI assay been approved by the FDA for use in aiding the diagnosis of acute myocardial infarctions[1]. However, these more sensitive assays allow for the reliable measurement of very low concentrations of cTnI, which are reflective of risk, even in the general population. Among middle-aged individuals without coronary heart disease, hs-cTnI is strongly associated with future cardiovascular risk[2,3].

Hs-cTnI levels are associated with age[2,4]; however, the prognostic implications of hs-cTnI in older adults has not been well-characterized. Prior work in ARIC has shown that its counterpart, high-sensitivity cardiac troponin T (hs-cTnT) improves risk prediction beyond traditional risk factors included in the Pooled Cohort Equation in older adults[5], suggesting that hs-cTnI may improve risk stratification as well. In middle-aged populations, both hs-cTnT and hs-cTnI are associated with cardiovascular and mortality risk[2]. However, despite being derived from a common protein complex in cardiomyocytes, hs-cTnI and hs-cTnT levels are only modestly correlated with one another[2,4] suggesting they may not be entirely exchangeable with one another.

Furthermore, there is ongoing controversy regarding the use of sex-specific cutpoints in interpreting hs-cTnI values[6]. Current package inserts for hs-cTnI advocate for the use of sex-specific cutpoints; however, whether this added complexity improves risk stratification compared to a common cutpoint remains debated.

Therefore, our objectives are to leverage the measurements of hs-cTnI available in ARIC at visit 5 to: 1) assess the associations of hs-cTnI with risk of cardiovascular disease and death; and 2) to assess whether there is added benefit of sex-specific cutpoints compared to common cutpoints.

5. Main Hypothesis/Study Questions:

We aim to assess the utility of hs-cTnI in the risk stratification of older participants over the age of 65 and assess the association of hs-cTnI with subsequent cardiovascular and mortality risk. We will also compare the prognostic power of risk categories defined using sex-specific cutpoints to those using common cutpoints.

Hypothesis 1: Hs-cTnI will improve cardiovascular and mortality risk stratification in older adults beyond traditional cardiovascular risk factors.

Hypothesis 2: Common cutpoints may perform similarly to sex-specific cutpoints in risk prediction models.

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: Prospective cohort study

Inclusion: All black and white participants at ARIC visit 5

Exclusions: We will apply the standard ARIC exclusions and exclude participants with missing hs-cTnI measurements.

Key exposures:

High-sensitivity troponin I was measured in stored frozen plasma samples on an Architect *i*2000sr analyzer using an Abbott Architect Stat Troponin I double chemiluminescent immunoassay (Abbott Park, IL), with a lower limit of detection of 1.2 ng/L.

Definitions of hsTnI:

a. Log2-transformed
b. Sex-specific cutpoints (women: <4, 4 to <10, ≥10ng/mL; men: <6, 6 to <12, ≥12ng/mL)
c. Common cutpoints (<6, 6 to <12, ≥12ng/mL)

Outcomes:

Among those without prevalent cardiovascular disease (ASCVD + heart failure)

1) Incident global cardiovascular event (MI, stroke, heart failure)
2) Component cardiovascular events
    a. MI or revascularization or Stroke (ASCVD)
    b. Heart failure

Among the full population:

3) Cardiovascular mortality
4) All-cause mortality

Important covariates: age, sex, race-center, total cholesterol, LDL, HDL, Triglycerides, SBP, DBP, hypertension medication use, cholesterol medication use, current smoking status, diabetes status

Analyses:

We will compare baseline characteristics by levels of hs-cTnI, using the definitions indicated above. We will use Kaplan-Meier survival analysis to compare the cumulative incidence of cardiovascular events and mortality by troponin categories independently and in combination. We will use Cox proportional hazards models to compare hazard ratios and corresponding 95% confidence intervals to characterize the association of troponin levels with cardiovascular risk and mortality with adjustment for relevant covariates. To assess the prognostic performance of these novel biomarkers, changes in the C-statistic and net reclassification improvement will be compared between models with the troponin measurement compared to those based on previously published risk equations.

Limitations:

1) Given the observational nature of ARIC, there is the possibility of residual confounding.
2) Participants may have troponin values below the lower limit of detection. For these participants, we will assign a value that is half the lower limit of detection for continuous analyses.

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/mantrack/maintain/search/dtSearch.html

___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)?

Proposal # 2775: High-sensitivity troponin I and incident heart failure hospitalization, myocardial infarction, stroke and cardiovascular disease mortality in ARIC (First Author: Christie Ballantyne)

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* ___2013.21, ____)
___ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.

References:

1. U.S. FDA Clears Abbott's High Sensitivity Troponin-I Blood Test That Aids Doctors in Diagnosing Heart Attacks Faster and More Accurately - Sep 25, 2019. https://abbott.mediaroom.com/2019-09-25-U-S-FDA-Clears-Abbotts-High-Sensitivity-Troponin-I-Blood-Test-That-Aids-Doctors-in-Diagnosing-Heart-Attacks-Faster-and-More-Accurately. Accessed October 24, 2019.
2. Jia X, Sun W, Hoogeveen RC, et al. High-Sensitivity Troponin I and Incident Coronary Events, Stroke, Heart Failure Hospitalization, and Mortality in the ARIC Study. *Circulation*. 2019;139(23):2642-2653. doi:10.1161/CIRCULATIONAHA.118.038772
3. Welsh P, Preiss D, Hayward C, et al. Cardiac Troponin T and Troponin I in the General Population: Comparing and Contrasting their Genetic Determinants and Associations with Outcomes. *Circulation*. 2019. doi:10.1161/circulationaha.118.038529
4. Welsh P, Preiss D, Shah ASV, et al. Comparison between high-sensitivity cardiac troponin T and cardiac troponin I in a large general population cohort. *Clin Chem*. 2018;64(11):1607-1616. doi:10.1373/clinchem.2018.292086
5. Saeed A, Nambi V, Sun W, et al. Short-Term Global Cardiovascular Disease Risk Prediction in Older Adults. *J Am Coll Cardiol*. 2018;71(22):2527-2536. doi:10.1016/j.jacc.2018.02.050
6. Giannitsis E. Potential concerns regarding the use of sex-specific cutpoints for high-sensitivity troponin assays. *Clin Chem*. 2017;63(1):264-266. doi:10.1373/clinchem.2016.254680