ARIC Manuscript Proposal #3273

PC Reviewed: 11/13/18   Status: _____   Priority: 2
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: Cross-sectional associations of sociodemographic factors and clinical biomarkers with concordant and discordant elevations in high-sensitivity troponins I and T

  b. Abbreviated Title (Length 26 characters): Cross-sectional associations with hs-troponins

2. Writing Group:
    Writing group members: Olive Tang; Kunihiro Matsushita; Josef Coresh; John W (Bill) McEvoy; A. Richey Sharrett; Christie Ballantyne; Ron Hoogeveen; 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:
The data for this proposal has been measured and will be available shortly for analysis. We will aim to conduct the analysis and draft the manuscript within 1 year of proposal approval and availability of data.

4. Rationale:

Despite population improvements in a number of cardiovascular risk factors, the prevalence of diabetes continues to increase, contributing to growing health and societal burdens[1–4]. There is growing recognition that the population with diabetes is not clinically uniform, and the implications of hyperglycemia may vary from person to person. Furthermore, new anti-hyperglycemic therapies (SGLT2 inhibitors and GLP1 agonists) with additional cardioprotective benefits beyond traditional medications are far costlier than established therapies. These new therapies have predominantly been tested in populations at elevated cardiovascular risk, defined based on a prior event or multiple traditional risk factors[5]. However, these traditional risk factors may not be adequate to identify and characterize subgroups at elevated cardiovascular risk for targeted therapy.

Advances in laboratory methods to identify previously undetectable levels of cardiac troponins have paved the way for the use of these high sensitivity measurements as markers of subclinical myocardial damage[6] and risk stratification in the general population. Elevations in high-sensitivity cardiac troponin T (hs-cTnT), at non-myocardial infarction levels, have been associated with increased risk of cardiovascular events, dementia[7], and mortality[8–10]. Elevations in high sensitivity cardiac troponin I (hs-cTnI) have been associated with left ventricular hypertrophy[11], reduced ejection fraction[11], diastolic dysfunction[11], cardiovascular events, and mortality[9].

Simultaneous measurements of hs-cTnT and hs-cTnI have been scarce, and little literature exists to inform potential differences between these two markers. In a study of the general Scottish population, Welsh et al. (2018) observed low correlation between hs-cTnT and hs-cTnI, with a robust association of diabetes with elevations in hs-cTnT, but not hs-cTnI[12].

Newly available measurements of hs-cTnI in ARIC provide the opportunity to compare the associations of sociodemographic and risk factor characteristics with both hs-cTnI and hs-cTnT in participants with diabetes, compared to the general population. Prior work in ARIC has demonstrated the association of hs-cTnT with markers of hyperglycemia[13–15] and emerging work by Jia et al. (Manuscript Proposal # 2775) demonstrate only a moderate correlation between hs-cTnT and hs-cTnI (r<0.60) in the ARIC population, suggesting the two troponin measures may be distinct and complementary biological indicators.

Even though both cardiac troponins are thought to be released with myocardiocyte damage, a number of distinct characteristics may contribute to discordances between the two measures. Compared to troponin T, troponin I is smaller, released more often as a part of a complex, is less stable, but thought to be more specific in the diagnosis of myocardial infarction[16]. Both molecules undergo renal clearance, but troponin T is larger and may be more susceptible to advanced glycation, which may impede its clearance[16]. Epidemiologically, early work suggests that diabetes may be more strongly associated with hs-cTnT, while cholesterol may be more strongly associated with hs-cTnI[12], suggesting hs-cTnT may be more reflective of microvascular damage as compared to hs-cTnI.

Here we propose assessing the associations of elevations in hs-cTnT and hs-cTnI, in isolation and in combination, with baseline sociodemographic characteristics and biomarkers at ARIC visit 4. Associations with sociodemographic factors can help identify potential at-risk groups in whom additional clinical attention may be warranted, while clinical biomarkers such as glycemic and renal function markers may be associated with discordance between these related

markers. We will assess whether the associated factors differ between those with diabetes and those without.

5. **Main Hypothesis/Study Questions**:

Study Questions:
1) What sociodemographic and clinical factors are associated with elevations in hs-cTnT and/or hs-cTnI in participants with diabetes?
2) Do these associations differ from those observed in those without diabetes?

Hypotheses:
1) There are shared risk factors associated with elevations in either hsTnT or hsTnI, such as age, however, there may be clinical factors, such as renal function and diabetes, which may be more strongly associated with elevations in hsTnT.
2) Glycemic and kidney function markers may be associated with discordance between hs-cTnT and hs-cTnI levels.

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 analysis of ARIC participants at visit 4

Inclusion/Exclusion: Standard ARIC exclusions will apply. Additionally, participants missing hs-cTnT and/or hs-cTnI will be excluded.

Exposure:

Exposure category	ARIC measurements
Demographic factors	Age
	Sex
	Race
Healthcare access	Have personal physician or clinic
	Health insurance
Traditional cardiovascular risk factors	Total cholesterol
	LDL cholesterol
	HDL cholesterol
	Triglycerides
	Systolic blood pressure
	Diastolic blood pressure
	Body mass index
	Current smoking
	History of coronary heart disease
	History of heart failure
	History of stroke
	Hypertension
	Cholesterol-lowering medication use
	Anti-hypertensive medication use
	Anti-hyperglycemic medication use

Biomarkers	*Glycemic markers*
	Glycated Albumin
	1,5-anhydroglucitol
	Fructosamine
	Blood glucose
	2h glucose
	Renal biomarkers
	eGFR (based on creatinine and cystatin c)
	Urine protein:creatinine ratio
	Beta2 microglobulin
	Beta trace protein
	Cardiac markers
	Hs-CRP
	NT-proBNP
	Gal-3
Other	Diabetes duration
	Left ventricular hypertrophy
	Carotid intimal medial thickness

Outcomes:

Hs-cTnT was measured in stored frozen plasma samples on a Cobas e411 analyzer using the Roche Elecsys Troponin T assay (Indianapolis, IN), with a lower limit of detection of 3ng/L. Hs-cTnI 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 1.2ng/L.

High sensitivity troponin levels will be defined as categorically:
1. Low hs-cTnT/low hs-cTnI
2. Low hs-cTnT/high hs-cTnI
3. High hs-cTnT/low hs-cTnI
4. High hs-cTnt/high hs-cTnI

Elevations in hs-troponins will be modeled:
1. Categorically (Table 1)
2. based on observed 99th sex-specific percentiles

Table 1. Reference values for hs-cTnT and hs-cTnI

	Reference Cutpoints	
	Men	Women
hs-cTnT[17]	< 50 years old: 14ng/mL 50-64 years old: 17ng/mL ≥ 65 years old: 31ng/mL	< 65 years old: 14ng/mL ≥ 65 years old: 17ng/mL
hs-cTnI	> 12ng/mL	> 10 ng/mL

Statistical approach: We will use one-way analysis of variance (ANOVA) to compare continuous variables and chi-squared tests for categorical variables. Logistic regressions will be used to model elevations in hs-cTnT and hs-cTnI. These analyses will be conducted separately for elevations in either hs-cTnT or hs-cTnI and for elevations in both markers. The magnitude of the

model coefficients will be used to assess the comparative strength of predictors for elevations in either marker.

Limitations:
1) Given the cross-sectional nature of the proposed analyses, we will not be able to assess temporality between the exposure characteristics and elevations in hs-troponin.
2) There will be reliance on single measurements of the cardiac biomarkers at visit 4 made in stored specimens.

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)

Proposal # 2707: Hypoglycemia and Subclinical Myocardial Damage in Older Adults with Diabetes (First Author: Alexandra Lee)

Proposal # 2765: Relationship of Blood Pressure Parameters with High Sensitivity Cardiac Troponin-T and N-Terminal Prohormone of Brain Natriuretic Peptide in the Elderly: The Atherosclerosis Risk in Communities Cohort Study (First Author: Nidhi Madan)

Proposal # 2129: Diabetes and prediabetes and the incidence and progression of subclinical myocardial injury (First Author: Elizabeth Selvin)

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.

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