ARIC Manuscript Proposal #3505

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

1.a. Full Title: Long-term high sensitivity cardiac Troponin T (hs-cTnT) change and the risk of incidence atrial fibrillation in the ARIC cohort

b. Abbreviated Title (Length 26 characters):

2. Writing Group:

Writing group members: Linzi Li, Ron C. Hoogeveen, Elizabeth Selvin, Lin Yee Chen, Elsayed Z. Soliman, Faye L. Norby, Alvaro Alonso, others welcome

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

First author: **Linzi Li**
Address: Dept of Epidemiology, Rollins School of Public Health
Emory University
1518 Clifton Rd NE
Phone: 404-513-9466 Fax:
E-mail: linzi.li@emory.edu

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).
Name: **Alvaro Alonso**
Address: Dept of Epidemiology, Rollins School of Public Health
Emory University
1518 Clifton Rd NE, CNR 3051
Atlanta, GA 30322
Phone: 404-727-8714 Fax:
E-mail: alvaro.alonso@emory.edu

3. Timeline:

A draft manuscript will be ready to submit for Publications Committee Review in spring 2020.

4. Rationale:

Atrial fibrillation (AF) is the most common chronic cardiac arrhythmia, with an estimated prevalence of 2.7 million adults in the United States in 2010. [1] In 2030, the prevalence is

expected to rise to 12.1 million.[1] AF is associated with increased mortality and morbidity, and can lead to severe complications, such as stroke, heart failure (HF) and chronic kidney disease (CKD). [1,2] [3,4] AF can be paroxysmal and is often asymptomatic, which creates obstacles for the detection and prevention of AF. Due to these limitations, investigators have developed and validated risk prediction models for AF, which can assist in identifying high-risk individuals.[5] [6] These models have moderate prediction abilities; however, addition of novel risk factor measurements may enhance the predictive ability of the models.

High sensitivity cardiac Troponin T (hs-cTnT) is a well-established biomarker of myocardial injury, which is used to diagnose acute myocardial infarction (MI).[7] Elevated hs-cTnT levels are also associated with incidence of other cardiovascular and chronic diseases, such as incident HF and CKD. [8,9] Prior studies have described the association between hs-cTnT and the risk of developing AF. In a Japanese general population without apparent cardiovascular disease, circulating hs-cTnT levels were greater among subjects with AF compared to those without AF.[10] In the ARIC study, the risk of incident AF was 1.16 times higher with each 1-standard deviation increase of ln(hs-cTnT) level. [11] In the Cardiovascular Health Study, a large prospective cohort of ambulatory older adults, hs-cTnT was significantly associated with incident AF beyond traditional risk factors. [12] The change in biomarker measures over time may be more informative than a 1-time measurement. In ARIC, the six-year change in hs-cTnT was independently associated with incident coronary heart disease (CHD), death and HF.[13] Our previous study on the change in NT-proBNP, another biomarker of AF risk, provided evidence that additional information on biomarker change can help improve the prediction of AF.[14] To our knowledge, little information is known about the impact of long-term hs-cTnT change on the risk of incident AF, as well as the role of hs-cTnT change in upstream mechanism of developing incident AF. With its repeated measurements of hs-cTnT and rigorously assessed AF endpoints, the large ARIC study is well suited for a study that explores the role of change in circulating hs-cTnT as a predictor of incident AF.

5. Main Hypothesis/Study Questions:

- To evaluate the association of medium and long-term change in circulating hs-cTnT with the risk of incident AF. We hypothesize that increases in circulating hs-cTnT will be associated with increased risk of AF.

- To determine the value of medium and long-term change in circulating hs-cTnT in the prediction of AF. We hypothesize that change in hs-cTnT will improve our ability to predict the risk of AF.

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. We will conduct two separate analysis. First, we will evaluate the association of change in hs-cTnT between visit 2 and visit 4 with the incidence of AF after visit 4. Second, we will evaluate the association of change in hs-cTNT between visits 2 and 5 with the incidence of AF after visit 5.

Inclusion and exclusion criteria

- Inclusion: ARIC participants who had circulating hs-cTnT measurements at both visit 2, visit 4 and/or visit 5 (depending on the analysis).
- Exclusion: participants who had developed AF at or before visit 4/5; those who had HF, CHD, or eGFR <60 mL/min/1.73 m2 at or before visit 4/5; non-whites from the Minneapolis and Washington County field centers, and individuals other than white or African American in the Forsyth County field center.

Exposure

The “medium-term” change of hs-cTnT between visit 2 and 4, “long-term” change of hs-cTnT between visit 2 and 5.

Outcome

Incident AF occurred from the end of visit 4/5 through 2017.

Covariates (all from visit 2)

Age, sex, race, BMI, smoking status, drinking status, SBP, LDL, HDL, ECG p wave terminal force in V1, triglycerides, diabetes, LVH, use of anti-hypertension medication, use of blood cholesterol medications, c-reactive protein, NT-proBNP, study center, eGFR.

Statistical analysis plan

We will first group individuals based on combinations of categories of hs-cTnT at visit 2 and visit 4: undetectable (<5ng/L), detectable (≥5ng/L, <14ng/L), elevated (≥14 ng/L)[13], as well as

increased and decreased concentrations of hs-cTnT between the two visits. The baseline characteristics of study population at visit 4 will be described based on these categories (mean [SD] for continuous variables and frequency [percentage] for categorical variables). The incidence of AF will be calculated in each group. Hs-cTnT level will also be natural logarithm-transformed (ln-transformed) and the main outcome variable will be the difference between the two ln-transformed variables at visit 2 and visit 4, which corresponds to the logarithm of the ratio [$\ln\left(\frac{hs-cTnT\ 4}{hs-cTnT\ 2}\right)$]. Additionally, we will model hs-cTnT change as percentage of relative change ($\frac{hs-cTnT\ 4 - hs-cTnT\ 2}{hs-cTnT\ 2}$). After exploring the distribution of this variable in the final sample, we will model it as a continuous variable. To minimize the effect of missing data of participants who were dead or loss to follow up, we will use multiple imputation by chained equations (MICE) to impute missing values. Then we will examine the association between the change of hs-cTnT and the risk of incident AF using Cox proportional hazards regression to estimate the hazard ratio (HRs) and 95% confidence intervals (CIs), in the following two models:

1) Only adjusted for age, sex and race
2) Fully adjusted for all the covariates listed above + visit 2 hs-cTnT level

The change of hs-cTnT will be modeled both as a continuous and a categorical variable.
Next, we will stratify the study sample by sex and race, and then graph the HRs and corresponding CIs in each strata to observe the difference between strata.
Finally, we will explore the predictive ability of change in hs-cTnT by adding it to the CHARGE-AF score, which is a risk prediction score for predicting incident AF. We will calculate the change in c-statistic and the net reclassification index. [15]
We will repeat the analyses using the change of hs-cTnT from visit 2 to visit 5 to compare if the "long-term" change predicts AF incidents better than the "short-term" change. We realize that the sample size will be a limitation since we will include the participants who lived through visit 5. We may report our results selectively in the manuscript.

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

_____ 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)?

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 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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2. Emdin CA, Wong CX, Hsiao AJ, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ.* 2016;532:h7013.
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