ARIC Manuscript Proposal # 1776

PC Reviewed: 4/8/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: High-Sensitivity Cardiac Troponin T and the Risk of Incident Atrial Fibrillation: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Troponin T and AF

2. Writing Group:

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

Data analysis – 4 months
First draft of the manuscript – 4 months

4. Rationale:

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia in clinical practice and is associated with substantial morbidity, mortality, and treatment costs (1). While a good body of information exists about risk factors for AF (2), its mechanism remains incompletely understood. Nishida and colleagues recently examined the mechanistic role of coronary artery occlusion in a canine model of chronic atrial tachyarrhythmias (3). Using this model, the authors found that chronic ischemia resulted in increased fibrosis, which in turn caused the development of the substrates for new AF and AF maintenance. Interventions that decrease ischemia may therefore have beneficial effects on the prevention and treatment of AF. These results also suggest that subclinical ischemia may play an important role in the risk stratification for AF.

Previous clinical and population-based studies have found that high-sensitivity cardiac troponin T (hs-cTnT), a marker of subclinical infarctions, is associated with an increased risk of structural heart disease (4), incident heart failure (5, 6), cardiovascular mortality (5, 6), and all-cause mortality (4, 7). However, the association between hs-cTnT and the risk of incident AF remains unknown, as does the role of hs-cTnT in the risk prediction and stratification for incident AF. The present study will address these questions using data from the Atherosclerosis Risk in Communities (ARIC) Study.

5. Main Hypothesis/Study Questions:

The primary objective of this study is to estimate the association between hs-cTnT and the risk of incident AF in participants of ARIC. The secondary objectives are to determine if this association differs with sex or race/ethnicity and to examine the predictive ability of hs-cTnT for incident AF.

Our hypotheses are that the risk of incident AF increases with increasing quintile of hs-cTnT and that the inclusion of hs-cTnT in a model with known clinical predictors of AF improves our ability to predict its occurrence.

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

We will examine the association between hs-cTnT and the risk of incident AF using a longitudinal analysis of ARIC. Hs-cTnT levels were assessed using stored plasma samples from ARIC visit 4; this visit will therefore serve as the baseline for the present study.

Inclusion/Exclusion

Exclusion criteria will include evidence of a history of AF at visit 4 (from study ECGs or prior hospital discharge codes from baseline up to visit 4), a missing or unreadable visit 4 electrocardiogram, and missing data for hs-cTnT or covariates. In addition, participants

from Minneapolis, MN or Washington County who reported a race/ethnicity other than Caucasian will be excluded, as will those from all sites who reported a race/ethnicity other than Caucasian or African American.

Exposure

Using plasma samples from ARIC visit 4, we measured hs-cTnT levels using Elecsys Troponin T (Roche Diagnostics, Indianapolis, IN), a novel high-sensitivity assay implemented on an automated Cobas e411 analyzer. The lower limit of detection is 0.003 µg/L. In a subpopulation of healthy subjects aged 20 to 70 years, the 99th percentile for this assay was 0.03 µg/L (Roche Diagnostics, data on file). The between-assay coefficient of variation was 2.6% and 6.9% for control materials with mean hs-cTnT concentrations of 2.378 µg/L and 0.029 µg/L, respectively. Analysis of 418 masked duplicate ARIC samples revealed a reliability coefficient of 0.98.

We will examine hs-cTnT as a continuous variable with appropriate transformation and accounting for left censoring. In addition, we will use appropriate categorization of participants based on the relationship seen in dose-effect curves, as well as a few default categories such as quintiles.

Outcome

Incident AF will be defined using previously described methods (2, 8-10). Briefly, hospitalizations were assessed during annual telephone follow-ups and review of local hospital discharge lists. Hospital discharge reports were abstracted, as previously described (11). Participants will be considered to have AF if their hospital discharge reports include ICD-9 codes for AF (ICD-9 code 427.31) or atrial flutter (ICD-9 code 427.32) or if AF is listed as the underlying cause of death on the death certificate (ICD-9 code 427.3 or ICD-10 code 148). AF occurring during hospitalizations for cardiac procedures, including heart revascularization surgery (36.X) or other cardiac surgery involving valves or septa (ICD-9 code 35.X) will not be considered events. The date of incident AF will be defined as the date of the first evidence of its occurrence, and only 1 event will be considered per participant. A total of 788 cases of incident AF occurred by the end of the 2007 ARIC follow-up.

Statistical Analysis

First, we will explore the dose-effect association between hs-TNT and incident AF using continuous measure of hs-TNT with left censoring using appropriate transformations such as natural log while allowing the relationship to take shapes per restricted cubic splines with knots at several percentile cut-points such as 25th, 75th, 90th, and 95th. We understand that about a third of the participants have concentrations below limit of detection. Also, we will calculate age-adjusted, sex-specific rates of AF for each hs-cTnT quintile and will compare rates across quintiles using 1-degree-of-freedom (df) tests for trends. Race/ethnicity-specific rates will be examined in a similar manner.

Our primary analysis will involve the construction of 3 Cox proportional hazards models to examine the association between hs-cTnT quintile and the rate of AF with varying degree of covariate adjustment. The first model will be minimally adjusted. The second

model will adjust for potential confounders, including age, sex, race, study center, level of education, smoking status, reported alcohol intake, body mass index, height, systolic blood pressure, use of antihypertensive medications, diabetes, high-sensitivity C-reactive protein (hsCRP), N-terminal pro b-type natriuretic peptide (NT-proBNP), prevalent coronary heart disease, and prevalent congestive heart failure. The third model will include time-dependent adjustment for incident cardiovascular disease using hospitalization data collected during annual follow-ups to examine its role as a potential mediator. We will use piecewise cubic splines to explore the distribution and shape of the association between hs-CTnT and the rate of AF risk. We will examine potential modification by sex and race/ethnicity by including multiplicative interaction terms in the Cox proportional hazards models, and stratified results will be presented if effect modification is present. In sensitivity analyses, we will examine the association in participants free of prevalent CHD or CHF at visit 4 and will adjust for use of anti-arrhythmic medications, including class 1 (sodium-channel blockers such as quinidine), class 2 (beta-blockers), class 3 (potassium-channel blockers such as amiodarone), and class 4 anti-arrhythmic agents (calcium-channel blockers). Visual assessment of log(log(survival)) plots will be used to assess the proportionality of hazards assumption.

If there is a significant association between hs-cTnT and the risk of AF, we will examine the predictive ability of hs-cTnT for incident AF in a two-step procedure. First, we will compute the area under the Receiver Operating Characteristic (ROC) curve (AUC) for Cox proportional hazards models (12) with and without hs-cTnT quintile. Second, we will calculate the net reclassification improvement (NRI) (13) and use reclassification tables (14-16) to examine the number of subjects whose predicted risk would be reclassified by adding hs-cTnT to a model of clinical AF predictors previously identified in ARIC (2). NRI will be examined with risk of AF treated categorically using cutoffs developed in the Framingham Heart Study (<5%, 5-15%, or >15% 10-year risk) (17), and incremental discrimination index (IDI) will be used to study reclassification with hs-cTnT treated continuously (13).

Limitations

There exists a number of potential limitations. First, since the baseline for this study will be ARIC visit 4, follow-up will be restricted to 1996-98 to 2007. With 788 incident cases of AF, the study will have ample power to address its primary object but the power to examine interactions may be modest. Second, there is the potential for misclassification, particularly in outcome assessment. Cases will be ascertained via hospitalization and death records, and we will therefore not capture asymptomatic cases of AF and those managed in outpatient settings. This misclassification is not expected to be associated with exposure status and thus should be non-differential. Finally, we are restricting our study to Caucasians and African Americans and therefore cannot generalize our results to those of different races/ethnicities.

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 ICTDER03 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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?

____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/search.php

__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 Numbers 1563, 1564, and 1732.

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* 2008.12**)**

___ 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.cscc.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.

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