ARIC Manuscript Proposal #2050

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

1.a. Full Title: The association of high-sensitivity cardiac troponin T and natriuretic peptide with incident end-stage renal disease: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): cTnT, NT-pro-BNP, & ESRD risk

2. Writing Group:

Writing group members: Yuhree Kim, Kunihiro Matsushita, Yingying Sang, Morgan Grams, Hicham Skali, Amil M. Shah, Ron C. Hoogeveen, Scott D. Solomon, Christie M. Ballantyne, Josef Coresh, others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. YK [**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 to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

As expressed in terms of cardiorenal syndrome or renocardiac syndrome, a close pathophysiological relationship between the kidney and heart is well known.[1-4] There are

several mechanisms linking kidney dysfunction to cardiovascular disease such as imbalance of salt and fluid, activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, endothelial dysfunction, inflammation, and oxidative stress.[1, 5-7] Indeed, numerous epidemiological studies have reported a higher risk of cardiovascular disease among those with kidney dysfunction or damage as compared to those without.[8-14]

In contrast, epidemiological data as to whether cardiac dysfunction predates kidney disease progression are actually sparse, probably because assessing cardiac function in epidemiological studies is expensive and cumbersome. A few small studies (n<500) have demonstrated that cardiac parameters (i.e., left ventricular ejection fraction and hypertrophy and left atrial diameter) are predictors for kidney disease progression.[12, 15] However, these studies investigated advanced CKD patients, and thus those cardiac manifestations may merely reflect long-lasting kidney dysfunction or its severity. A collaborative analysis of two community-based cohorts demonstrated a higher risk of kidney disease progression among those with history of cardiovascular disease as compared to those without at baseline.[16] However, these results can be confounded by treatment or clinical examinations, which are likely to be provided to those with cardiovascular disease and are potentially harmful to the kidney (e.g., diuretics or iodinated contrast).

In this context, there are a few circulating markers that reflect cardiac function or damage such as high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro–B-type natriuretic peptide (NT-pro-BNP). These two cardiac markers may capture cardiac damage or dysfunction even before they can be detected by imaging modalities.[17] A study using a subsample (n~1,000) from the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) have demonstrated that these cardiac markers are independently associated with risk for end-stage renal disease (ESRD).[18] However, every participant in this study had CKD (as well as type 2 diabetes and anemia) at baseline, and the prevalence of clinical cardiovascular disease was high (>50%), leaving uncertainty in a prospective association of cardiac dysfunction with the development of kidney disease, particularly in the general population. Therefore, the objective of this study is to investigate the associations of hs-cTnT and NT-pro-BNP and ESRD risk in a community-based cohort, the Atherosclerosis Risk in Communities (ARIC) Study. We are particularly interested in the associations among those without clinical cardiac disease and reduced kidney function at baseline. A larger sample size in the ARIC Study would also allow us to conduct stratified analyses according to key clinical factors such as diabetes to extend our knowledge on this topic.

5. Main Hypothesis/Study Questions:

Hypothesis : Novel cardiac damage marker (hs-cTnT) and cardiac overload marker (NT-pro-BNP) will be associated with ESRD risk independent of conventional cardiovascular and kidney risk factors in the general population.

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).

Inclusions:
- All African American and white ARIC participants who attended visit 4 (1996-1998) (the only visit at which hs-cTnT and NT-pro-BNP are available)
- Individuals with data on hs-cTnT & NT-pro-BNP

Exclusions:
-Race/ethnicity other than African American or white
-Individuals without data of hs-cTnT and NT-pro-BNP
-Prevalent ESRD and CKD stage 5 (kidney failure) at visit 4 (incident ESRD cases between visit 1 and visit 4 and eGFR<15 at visit 4)

Exposure: Novel cardiac biomarkers

(1) hs-cTnT

hs-cTnT was measured by a novel highly sensitive assay with a lower limit of detection of 0.003 μg/L.

(2) NT-pro-BNP

NT-pro-BNP was measured by an electrochemiluminescent immunoassay with lower limit of detection 5 pg/mL

Outcome (All ESRD events that occurred after visit 4 and before January1, 2009 will be included)**:**
Incident ESRD was defined as hospitalization with ICD-9 codes for kidney transplant (V42.0) or dialysis (V45.1) or a procedural code indicating dialysis (hemodialysis, 39.95; or peritoneal dialysis, 54.98) or death with kidney failure (584.5-587). We would only include death with codes for acute renal failure (codes 586, 584, and 788.9) as ESRD for those with an earlier diagnosis of CKD (defined as eGFR <60 mL/min/1.73 m^2 and/or hospitalization code). However, individuals who had a dialysis code and an acute renal failure code without previous CKD and those with an acute renal failure code of 958.5 (traumatic anuria) were not included.[19]

Potential confounders:
-Sociodemographics: age, sex, race, education level
-Physical information: body mass index, blood pressure
-Lifestyle: smoking status, alcohol habit
-Comorbidities: history of cardiovascular disease (coronary heart disease [CHD], stroke, and heart failure [HF]), dyslipidemia (total cholesterol and HDL cholesterol), diabetes, hypertension (use of antihypertensive drugs or blood pressure ≥140/90 mmHg), kidney function (estimated glomerular filtration rate [eGFR]) and damage (albuminuria) at baseline

Statistical Analysis:
Baseline characteristics were summarized according to hs-cTnT and NT-pro-BNP levels. As previously done in the ARIC Study[20], hs-cTnT will be categorized into five groups based on undetectable level and a threshold for clinical elevation (corresponding to the 99th percentile value in healthy individuals specified by the manufacturer) (undetectable, 0.003-0.005 μg/L, 0.006-0.008 μg/L, 0.009-0.013 μg/L, and ≥0.014 μg/L). NT-pro-BNP

will be categorized into its quintiles. The relationship between baseline hs-cTnT and NT-pro-BNP levels was assessed using Spearman correlation coefficient.

The primary analysis will use Cox proportional hazards models to quantify the association of hs-cTnT and NT-pro-BNP with incident ESRD. These cardiac markers will be treated as categorical (aforementioned five groups) and continuous variables with splines respectively (knots at thresholds defining the five groups) in the models. We will adjust for the covariates listed above. In continuous variable analysis, for those with undetectable levels of the cardiac markers, we will assign half of the lower limit of detection for each marker. We will repeat the analysis after stratifying the study sample by age, sex, race, and presence/absence of comorbidities such as diabetes, hypertension, reduced eGFR, high albuminuria, and history of cardiac disease (CHD and HF).

We will implement four models for the adjustment for covariates. Model 1 will be crude. Model 2 will be adjusted for demographic variables, i.e., age, sex, and race. Model 3 will be further adjusted for known cardiovascular and kidney risk factors, i.e., systolic blood pressure, antihypertensive medication, smoking, alcohol intake, level of education, body mass index, total and HDL cholesterols, diabetes, history of cardiovascular disease. Model 4 will be further adjusted for kidney disease measures (eGFR and albuminuria) at baseline.

We will conduct a few sensitivity analyses. First, we will examine ESRD occurring in the absence of clinical cardiac disease. To accomplish this, we will conduct our analysis excluding those with prevalent CHD and HF at baseline and censoring incident CHD and HF cases that occurred prior to the date of ESRD. Second, since death can act as a competing endpoint of ESRD, we will conduct competing risk analysis.

Limitations:
There are ~200 ESRD cases after visit 4, and statistical power may be an issue for some stratified analyses. We have only single measurements of hs-cTnT and NT-pro-BNP. The threshold for initiation of kidney replacement therapy varies substantially across age and regions. So, the generalization of our findings should be done with caution. Lastly, we will not be able to rule out the possibility of residual confounding.

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

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)?
There are no proposals investigating the association of hs-cTnT and NT-pro-BNP with kidney outcomes including incident ESRD in ARIC.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __x__ 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 http://www.cscc.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.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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