ARIC Manuscript Proposal #2217

PC Reviewed: 9/10/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The association of NH_2-terminal pro–brain natriuretic peptide and high-sensitivity cardiac troponin T with incident acute kidney injury: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): hs-cTnT, NT-proBNP, & AKI risk

2. Writing Group:

Writing group members: Yuhree Kim, Kunihiro Matsushita, Yingying Sang, Morgan Grams, Hicham Skali, Amil M. Shah, Ron C. Hoogeveen, Elizabeth Selvin, 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]**

First author: Yuhree Kim
Address: Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street, Baltimore, MD 21205
Phone: 443-760-1835
E-mail: yuhkim@jhsph.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: Kunihiro Matsushita
Address: Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street (Rm W6017), Baltimore, MD 21205
Phone: (443) 287-8766 Fax: (443) 683-8358
E-mail: kmatsush@jhsph.edu

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:

Acute kidney injury (AKI) is an important clinical and public health issue.[1] A recent meta-analysis has reported that one in five adult patients experience AKI during

hospitalization worldwide,[2] and the incidence of the acute kidney injury (AKI) is growing[3]. Of importance, AKI is associated with poor prognosis during hospitalization and longer hospital stay.[4, 5]

Patients with cardiac disease are particularly at high risk of AKI. A study reports that 40% of patients who underwent cardiac surgery develop AKI.[6-9] AKI is also a common and critical complication for those with acute heart failure or acute coronary syndrome.[10, 11] The potential underlying mechanisms linking cardiac disease to subsequent AKI include alteration in hemodynamics[12, 13], neurohormonal activation[14], and nephrotoxic agents.[6, 15, 16]

In this context, a few small studies have demonstrated that higher levels of cardiac biomarkers, cTnT and BNP, are predictors of incident AKI among those who underwent surgery or revascularization[17-19]. However, whether this association holds in the general population in a longer term or not is unknown. If does, it may have etiological implications on the link between cardiac abnormality and AKI. Also, these markers may be useful to identify individuals at high risk for AKI in the community. Therefore, the objective of this study is to investigate the associations of hs-cTnT and NT-proBNP with AKI risk in a community-based cohort, the Atherosclerosis Risk in Communities (ARIC) Study.

5. Main Hypothesis/Study Questions:

Hypothesis : Cardiac damage marker (hs-cTnT) and cardiac overload marker (NT-pro-BNP) will be associated with AKI 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 2 (1990-92) or visit 4 (1996-1998) (the visits 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, NT-pro-BNP and other covariates
- CKD stage 5 (kidney failure) at visit 4 (eGFR<15ml/min per 1.73m^2)

Exposure: Cardiac biomarkers (Given that albuminuria, a potent predictor of AKI[20], is only available at visit 4, we will use visit 4 data for primary analysis and visit 2 data for secondary analysis with longer follow-up time and more AKI events.)

(1) hs-cTnT

hs-cTnT was measured by a novel highly sensitive assay with a lower limit of measurement of 3 ng/L.

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

Outcome (All AKI events that occurred after visit 2 or visit 4 and before December 31, 2010 will be included)**:**
Incident AKI was defined as hospitalization with AKI as well as death with AKI. Patients were classified with AKI if the discharge diagnosis contained an AKI-defining code, ICD-9-CM codes 584.5-584.9 or ICD-10-CM codes N17.0-17.9, or if the patient died during hospitalization and the associated death certificate listed AKI as a cause of death.[20]

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 only at visit 4) at baseline

Statistical Analysis:
As previously done in the ARIC Study[21], hs-cTnT will be grouped into five categories based on undetectable level and a threshold for clinical elevation (corresponding to the 99th percentile value in healthy individuals specified by the manufacturer) (unmeasurable, 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 five categories corresponding to the same percentiles of each categories of hs-cTnT. Baseline characteristics will be summarized according to these five categories of hs-cTnT and NT-pro-BNP. As some think 0.005 μg/L as more appropriate limit of detection for hs-cTnT[22], we will repeat analysis using the following five categories: <0.005 (undetectable), 0.005, 0.006-0.008, 0.009-0.013, and ≥0.014 μg/L. NT-pro-BNP will be also analyzed according to its quintiles and clinical thresholds[23]. The correlation between hs-cTnT and NT-pro-BNP levels will be assessed using Spearman correlation coefficient.

We will use Cox proportional hazards models for the primary analysis to quantify the association of hs-cTnT and NT-pro-BNP with incident AKI. These cardiac markers will be treated as categorical (aforementioned five groups) and continuous variables with linear 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 unmeasurable levels of the cardiac markers, we will assign half of the lower limit of measurement for each marker. We will implement five 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. Finally, Model 5 will be further adjusted for the opponent cardiac marker (i.e., hs-cTnT in the analysis of NT-proBNP, and NT-proBNP in the analysis of hs-cTnT).

We will conduct a few sensitivity analyses. First, we will repeat the analysis after stratifying the study sample by age, sex, race, smoking status, BMI and presence/absence of comorbidities such as diabetes, hypertension, history of cardiac disease (CHD and HF), reduced eGFR, high albuminuria, and chronic kidney disease (defined as eGFR <60 mL/min/1.73m^2 or ACR ≥30 mg/g). Second, we will examine AKI 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 or HF that occurred prior to the date of AKI. Lastly, since death can act as a competing endpoint of AKI, we will conduct competing risk analysis.

Limitations:
Incident AKI is defined by ICD codes and death certificate and thus might miss mild cases. The findings may not be generalizable to races/ethnicities other than blacks or whites. As true in any observational studies, 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 incident AKI in ARIC. The following proposal is investigating their associations with another kidney outcome, end-stage renal disease: #2050: The association of high-sensitivity cardiac troponin T and natriuretic peptide with incident end-stage renal disease: the Atherosclerosis Risk in Communities Study; Kim,Y. Key authors of this proposal are included in the present proposal as well.

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

_X__ A. primarily the result of an ancillary study (list number* 2009.16 (PI: Selvin) and 2008.10 (PI: Ballantyne))

___ 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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