ARIC Manuscript Proposal #2444

PC Reviewed: 10/14/14 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Blood biomarkers as predictors of end-stage renal disease and mortality – meta-analysis

b. Abbreviated Title (Length 26 characters): Biomarkers Meta-analysis

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

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3. Timeline:

Data available: Data are currently available
Projected date for first draft: November 2014
Projected date for initial submission to a journal: January 2015

4. Rationale:

Identification and validation of biomarkers to improve the prediction of clinically important outcomes of chronic kidney disease (CKD) over and above current biomarkers and existing clinical risk factors is a major goal of the CKD Biomarker Consortium. As part of our work in this consortium as well as other work we have observed that BTP and/or B2M are independently associated with increased risk of all-cause mortality and ESRD in general population-based samples (ARIC and NHANES), high-risk cohorts (patients with type 2 diabetes), as well as CKD-based cohorts (AASK, MDRD, and CRIC).[1-6] Across the published reports, there appear to be differences between the 2 markers in terms of their associations with mortality vs ESRD, in that B2M has stronger associations with mortality and BTP has stronger associations with ESRD. However, there are differences in analyses among the studies which does not allow direct comparison of the results. A meta-analysis allows rigorous comparison of the associations across populations and also increases power to observe associations. In addition, there is now a GFR estimating equation for BTP and B2M that allows these markers, and their combination, to be compared on the same scale as creatinine and cystatin C. In this manuscript, we will evaluate and compare the association of blood biomarkers (specifically BTP and B2M) with ESRD and mortality across the populations.

5. Main Hypothesis/Study Questions:

Our aim is to evaluate and compare the blood biomarkers BTP and B2M for their prediction of ESRD and mortality across general population, high risk and CKD cohorts. We hypothesize that BTP and B2M are associated with ESRD and mortality independent of known risk factors and the combination of these with established markers will have strongest associations with these outcomes will improve overall risk prediction **beyond** eGFRcr, the current clinical standard.

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: Meta-analysis of six prospective cohort studies (NHANES III, ARIC, Pima, AASK, MDRD Study, and CRIC).

Exclusion Criteria: Missing serum filtration marker measurements (creatinine, cystatin C, BTP, B2M), missing data on outcomes or multivariable model covariates.

Variables of Interest:

- **Primary predictors/exposures:** Estimated GFR from BTP , B2M, creatinine and cystatin – alone and in combination with each other
- **Outcomes:** ESRD, all-cause mortality
- **Covariates (baseline measures):** Age, sex, race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, other), BMI, smoking status (current, former, never), prevalent cardiovascular disease, hypertension, systolic blood pressure, diastolic blood pressure, diabetes, fasting glucose, hemoglobin A1c (HbA1c), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, lipid-lowering medication use, high sensitivity C-reactive protein (CRP), urinary albumin to creatinine ratio (UACR) or urine protein, creatinine-based eGFR (eGFRcr), cystatin C-based eGFR (eGFRcys), creatinine and cystatin C-based eGFR (eGFRcr-cys).

Summary of Data Analysis

- Analyses will first be conducted within each study and were then meta-analyzed across studies using random-effects models
- Within each study cox proportional hazards models to estimate the association of estimated GFR using each blood biomarker alone as well as eGFR of the combination of the four markers with each outcome.
- Models will be adjusted for (1) age, sex, race/ethnicity; (2) multivariable adjusted for potential demographic and clinical confounders; 3a) multivariable adjusted + eGFRcr (3b) multivariable adjusted + eGFRcys (3c) multivariable adjusted + eGFRcr-cys
- Splines will be used to assess for nonlinearity in each model
- HR will be expressed per 30 ml/min/1.73 m^2 of eGFR from 15 to 120 with a reference point at 95 ml/min/1.73 m^2 (50 ml/min/1.73 m^2 for the CKD cohorts for mortality and 65 ml/min per 1.73m2 for ESRD)[7]
- Seemingly unrelated regression will be used to compare HR across the markers.
- Heterogeneity to be evaluated using I statistic
- We will also cross-tabulate eGFR by each equation using clinical categories (≥90, 60-89, 45-59, 30-44, 15-29, <15 ml/min/1.73m^2) and evaluated the proportion of participants within each $eGFR_{cr}$ category that was reclassified by $eGFR_{BTP,}$ $eGFR_{B2M}$ and $eGFR_{4Markers}$. For each outcome, we will use multivariable Cox proportional hazards models to assess risks for adverse outcomes among participants who were reclassified upward (to higher $eGFR_{BTP,}$ $eGFR_{B2M}$ and $eGFR_{4Markers}$ categories) or downward (to lower $eGFR_{BTP,}$ $eGFR_{B2M}$ and $eGFR_{4Markers}$ categories) compared to participants with concordant eGFR classification[8].
- Overall improvement in reclassification based on clinical eGFR categories will be assessed applying net reclassification improvement (NRI)[9]. To assess generalizability, we will calculate NRI in subgroups according to age (<65 and

≥65 years old), sex, and race/ethnicity; diabetes and hypertension status; and by eGFR and albuminuria categories.

Limitations or Challenges

- Serum markers of interest measured once at baseline
- Meta-analysis across heterogeneous populations with differences in level of GFR, therefore difference in risk by level of eGFR may reflect study level differences
- eGFR based on BTP and B2M was developed in populations with CKD and accuracy in general population samples is not known

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/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)?

#2225 - Change in kidney filtration markers and risk of kidney disease, cardiovascular disease, and all-cause mortality: Atherosclerosis Risk in Communities Study

#2202 – Novel kidney filtration markers and incident sudden cardiac death: the Atherosclerosis Risk in Communities (ARIC) Study

#1944 – Risk factors for acute kidney injury

#2183 – Progression of CKD focusing on kidney function

#1574 – Comparison of novel markers of kidney function and prediction of cardiovascular events, mortality, and kidney failure: the Atherosclerosis Risk in Communities (ARIC) Study

#1581 – Novel markers of kidney function and prediction of incident chronic kidney disease and end-stage renal disease: the Atherosclerosis Risk in Communities (ARIC) Study

#1395 – Change in kidney function and coronary heart disease, stroke, and all-cause mortality: the Atherosclerosis Risk in Communities (ARIC) Study

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* 2009.16, 2006.16**)**

___ 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.