ARIC Manuscript Proposal # 3090

PC Reviewed: 12/12/17 Status: _____ Priority: 2
SC Reviewed: _________ Status: _____ Priority: _____

1.a. Full Title: Blood Pressure and its Potential Interaction with Natriuretic Peptide for Risk of End Stage Renal Disease

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

2. Writing Group:
Writing group members: Albert Danso Osei, Junichi Ishigami, Shoshana Ballew, John W. McEvoy, Morgan Grams, Josef Coresh, Vijay Nambi, Ron C. Hoogeveen, Christie M. Ballantyne, Elizabeth Selvin, Kunihiro Matsushita

I, the first author, confirm that all the co-authors have given their approval for this manuscript proposal. _ADO_____ [please confirm with your initials electronically or in writing]

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3. Timeline: Data to be used are already available. Analyses and manuscript preparation will be done over the next 6 months.

4. Rationale:
Hypertension is recognized as one of the most important risk factors for cardiovascular events\(^1\)\(^-\)\(^4\) and all-cause mortality given its high global prevalence and modifiable nature.\(^2\) Hypertension is also an important cause of end-stage renal disease (ESRD) globally\(^2\). However, data quantifying
the association of full spectrum of blood pressure levels (including low, normal, and high) with ESRD risk in the general population are surprisingly sparse. Understanding this association is clinically important since the American Heart Association and the American College of Cardiology just revised the definition of normal blood pressure, elevated blood pressure, and hypertension.

Also, a few studies have reported a J-shaped association between blood pressure and mortality. This pattern has not yet been extensively confirmed for ESRD, but again data in the general population are lacking. Of importance, a secondary analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) showed a higher incidence of kidney disease progression in the intensive blood pressure control group vs. the conventional control group, although achieved blood pressure level on treatment and untreated blood pressure level may have different implications for outcomes. Nonetheless, reduced peripheral perfusion due to cardiac dysfunction have been considered main reasons linking lower blood pressure to adverse health outcomes. Some investigators are trying to explore this aspect by investigating potential interaction of blood pressure and natriuretic peptide for clinical outcomes, but this potential interaction has not been systematically evaluated for ESRD.

Therefore, using data from the Atherosclerosis Risk in Communities (ARIC) Study, we aim to first quantify the association of the full spectrum of blood pressure with ESRD risk and then to explore a potential interaction of blood pressure and natriuretic peptide, NT-proBNP, for ESRD, with a main interest in participants with low blood pressure and high NT-proBNP (suggestive of subclinical cardiac dysfunction).

5. Main Hypothesis/Study Questions:
- Blood pressure will demonstrate a J-shaped association with ESRD, as shown for mortality.
- Individuals with low blood pressure plus high NT-proBNP levels will have particularly a high risk of ESRD, and thus NT-proBNP would be helpful to differentiate distinct groups of individuals with low blood pressure (normal blood pressure vs. low blood pressure due to cardiac dysfunction).

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 any of visit 2 (1990-1992), visit 4 (1996-98), and visit 5 (2011-13). Since ESRD is a relatively rare event, our primary analysis will be based on visit 2. Visit 4 will be useful to confirm robustness of our finding, and visit 5 will provide unique opportunity to explore specific patterns in older adults.
- Individuals with data on blood pressure and NT-pro-BNP

Exclusions:
- Race/ethnicity other than African American or white
- Individuals without data of blood pressure, NT-pro-BNP, ESRD, or key covariates
- Prevalent ESRD or glomerular filtration rate (GFR) <15 ml/min/1.73m² at relevant baseline visit
Exposure:
1. Blood Pressure
   Sitting systolic and diastolic blood pressure measured by a sphygmomanometer. Pulse pressure (systolic blood pressure minus diastolic blood pressure) will be analysed secondarily.
2. NT-pro-BNP
   NT-pro-BNP was measured by an electrochemiluminescent immunoassay with lower limit of detection 5 pg/mL

Outcome: ESRD
All ESRD events occurring after relevant baseline visit and before December 31, 2014 will be included. Incident ESRD will be defined as initiation of dialysis therapy, transplantation, or death due to kidney disease\(^1\). Cases with dialysis therapy and transplantation will be identified by linking them to the US Renal Data System (USRDS)\(^2\)

Potential Confounders:
- Sociodemographic: age, sex, race
- Physical information: body mass index
- 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, use of antihypertensive drugs, estimated GFR.

Statistical Analysis:
- The baseline characteristics will be summarized according to clinical categories or quantiles of blood pressure and NT-pro-BNP levels.
- The association of blood pressure with incident ESRD will be quantified by Cox proportional hazards models.
- Adjustment for the covariates listed above will be done in a graded fashion. Model 1 will be crude. Model 2 will be adjusted for demographic factors such as age, sex, race. Model 3 will be additionally adjusted for lifestyle factors such as smoking status. Model 4 will be further adjusted for comorbidities such as history of cardiovascular disease, dyslipidemia, diabetes, use of antihypertensive drugs, body mass index and estimated GFR.
- Any potential interaction between blood pressure and NT-proBNP for the risk of ESRD will be tested with a likelihood ratio test contrasting models with vs. without product terms of blood pressure and NT-proBNP. We will test interaction across Models 1-4 described above. To seek clinically relevant implications, potential interactions will be primarily based on categories of blood pressure and NT-proBNP but will be secondarily evaluated with them as continuous variables.
- We will perform a few sensitivity analyses. First, we will explore whether results are consistent across several demographic and clinical subgroups. We are particularly interested in those with and without antihypertensive drugs. Interaction will be tested with likelihood ratio test. Second, we will model blood pressure as a time-varying exposure using data from visits 2-5. Third, we will replace NT-proBNP with another representative cardiac marker, high-sensitivity troponin T.
Finally, competing risk analysis will be conducted since death can act as a competing endpoint of ESRD.

**Limitations:**
The number of ESRD may be an issue for some subgroups in stratified analyses. Results may not be simply generalizable to racial/ethnic groups other than whites and blacks. As any observation studies, there is 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    ___X___ 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](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 several proposals exploring risk factors for ESRD risk. However, to our knowledge, none of them extensively focus on blood pressure. Probably, a study proposal (#2050) that investigated the association of hs-cTnT and NT-pro-BNP with incident ESRD is most relevant. The manuscript from MP2050 was already published, and the interaction with blood pressure was not extensively evaluated. Also, key authors from that proposal are included in the current proposal.

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.cscu.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.cscu.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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _x___ No.

REFERENCES


"NTproBNP and incident cardiovascular events across systolic blood pressure (SBP) categories in the Atherosclerosis Risk In Communities (ARIC) study” –in preparation
