ARIC Manuscript Proposal #2031

PC Reviewed: 11/12/12   Status: <u>A</u>   Priority: <u>2</u>
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: Interaction of Kidney Disease Measures with Diabetes and Hypertension on Cardiovascular Disease: the Atherosclerosis Risk in Communities (ARIC) Study

  b. Abbreviated Title (Length 26 characters): **CKD-DM/HTN interaction on CVD**

2.   Writing Group:
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     Others are welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. <u>N.A.</u> **[please confirm with your initials electronically or in writing]**

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3. **Timeline**:
Completion of this project will occur within the next 6 months.

4. **Rationale**:
    Diabetes mellitus and hypertension are two of the leading risk factors for chronic kidney disease (CKD) [1,6-11]. Diabetes accounts for 40% of incident end-stage renal disease (ESRD) cases, while approximately 30% of ESRD cases are due to hypertension [12]. The contributions of diabetes and hypertension to kidney disease have led to recommendations for CKD screening among those with these conditions [13-16].
    Diabetes and hypertension are also important risk factors for cardiovascular disease (CVD) [6-11 19]. Compared to adults without diabetes, the risk of CVD among adults with diabetes is 2 to 4 times higher [6]. Similarly, each 20 mmHg higher systolic blood pressure contributes to ~2 fold higher risk of CVD [20]. Of note, CVD is one of the most important complications of CKD, as individuals with CKD are more likely to die due to CVD than reach ESRD [2, 21,23]. Thus, diabetes, hypertension, and CKD are tangled regarding their associations with CVD. However, very few studies have formally evaluated the interaction of CKD with diabetes and hypertension on specific CVD outcomes.
    In this context, the CKD Prognosis Consortium has recently investigated whether the association of kidney disease measures (estimated glomerular filtration rate [eGFR] and albuminuria) with cardiovascular mortality (along with all-cause mortality and ESRD) is consistent or not according to the presence and absence of diabetes mellitus and hypertension [18,19]. They observed that the contribution of these two kidney measures to cardiovascular mortality is largely similar regardless of diabetes status but is weaker among hypertensives as compared to non-hypertensives [18,19]. However, mortality can be affected by the healthcare system or the differential selection of treatment in subgroups by diabetes or hypertension status, and thus from an etiological point of view, it is also important to investigate their interactions for incident CVD including non-fatal cases. Furthermore, given that the contribution of CKD, diabetes, and hypertension to individual CVDs (e.g., coronary heart disease, stroke and heart failure) is not necessarily homogeneous, an evaluation of each CVD would be an added contribution to the existing body of knowledge [21,23].

5. **Main Hypothesis/Study Questions**:

    Do the associations of two key measures of kidney disease, eGFR and albuminuria, with CVD vary according to diabetes and hypertension status?

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).

Inclusion:

All study participant with data on key exposures (eGFR [serum creatinine, age, gender, and race] and albuminuria) and potential effect modifiers (diabetes and hypertension status) at visit 4.

Exclusion:

Persons who are not white or black will be excluded.
Individuals with missing data for covariates

Exposure: CKD measures

eGFR: GFR will be estimated by the CKD-EPI equation with serum creatinine [17]. Given its stronger associations with cardiovascular outcomes, we will also assess eGFR using cystatin C as a sensitivity analysis.

Albuminuria: As recommended in clinical guidelines, urine albumin-to-creatinine ratio (UACR) will be used as a measure of albuminuria [20].

Potential effect modifiers:

Diabetes will be defined by self-reported physician diagnosis or use of glucose lowering medications or a fasting blood glucose $\geq$126 mg/dl. Hypertension will be defined by a systolic blood pressure $\geq$140mmHg and a diastolic blood pressure $\geq$90 mm Hg, or use of antihypertensive medications.

Outcomes

The outcomes of interest will include coronary heart disease, stroke, and heart failure. Coronary heart disease includes a hospitalized myocardial infarction, fatal coronary disease, and cardiac procedure. Stroke will include definite and possible incident stroke. Heart failure will be defined as heart failure hospitalization or death from heart failure coded 428 according to the ICD-9 or I50 for ICD-10. Given that CVD is the leading cause of death in the US, we will also investigate all-cause mortality. To maximize statistical power for stratified analysis, we will also assess composite CVD outcomes (coronary disease, stroke, and heart failure).

Potential confounders:

Age, gender, race, body mass index, education level, smoking, cholesterol, triglycerides, history of cardiovascular disease at baseline, and alcohol consumption.

Analysis Plan:

We will conduct a series of subgroup analyses stratifying by diabetes and hypertension status to see if the associations between kidney measures and CVD are consistent in no diabetes vs. diabetes and no hypertension vs. hypertension. Cox proportional hazards model will be used to estimate CVD risk according to eGFR and ACR among persons with and without diabetes and hypertension. eGFR and UACR will be first modeled as continuous variables with splines (knots at 45, 60, 75, 90, 105 mL/min/1.73 m^2 for eGFR and at 10, 30, and 300 mg/g for UACR). To assess for effect modification two approaches will be used: 1) using a model with and without product terms of the CKD measures and hypertension and diabetes, we will evaluate the ratio of

hazard ratio between subgroups, reflecting multiplicative interaction, at each 1-unit of eGFR and ACR; and 2) using the same models, overall interaction will be tested by the likelihood ratio test. Subgroup analyses on age; less than 65 vs. ≥65, race; black vs. white, and gender; males vs. females will be conducted to assess the consistency of diabetes- and hypertension-kidney interaction on CVD risk. We will also assess 3-way interaction among kidney measures, diabetes, and hypertension.

Limitations:
We will not be able to rule out the possibility of residual confounding.
The single measure of serum creatinine and ACR might be another limitation.
Statistical power may be an issue when we analyze each CVD separately (particularly stroke).

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)?
MP1123: Albuminuria and kidney function as predictors of cardiovascular events mortality; Astor, B.

MP1362: Chronic kidney disease and risk of end-stage renal disease: The Atherosclerosis Risk in Communities Study; Bash, L.

MP1449: Comparison of a novel equation for estimated glomerular filtration rate with a conventional one regarding the association with coronary heart disease, stroke, and all-cause mortality: The Atherosclerosis Risk in Communities (ARIC) Study; Matsushita, K.

MP1823, "Interaction of chronic kidney disease with classical cardiovascular risk factors. Pooled analysis of general population cohorts"; Matsushita K.

These would be most relevant proposals. However, MP1123, 1362, and 1449 do not focus on interaction, and MP1823 does not deal with non-fatal CVD. Also, the key authors of these proposals are included in this 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.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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