ARIC Manuscript Proposal # 1823

PC Reviewed: 8/9/11      Status: A      Priority: 2
SC Reviewed: __________  Status: ____    Priority: ____


b. Abbreviated Title (Length 26 characters): CKD-CVD risk interaction

2. Writing Group:
Writing group members:
Kunihiro Matsushita, Ron Gansevoort, Brad C. Astor, Mark Woodward, Josef Coresh, and others for the CKD prognosis consortium.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. K.M. [please confirm with your initials electronically or in writing]

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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:
In 2002, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) defined and classified chronic kidney disease (CKD). CKD has been defined
as either albuminuria of ≥30mg/day or a decreased renal function (glomerular filtration rate [GFR] <60 ml/min/1.73 m²). Approximately 10-16% of the general population is estimated to have CKD. The prevalence of chronic kidney disease is especially high in the elderly, affecting >40% of people over the age of 70 years. Similarly the prevalence of CKD is higher in subjects with diabetes and hypertension. Moreover, as is true for other cardiovascular risk factors, the prevalence of CKD varies according to race and gender. In case of hypertension, there is evidence suggesting that hypertension is both a cause and a consequence of CKD.

In 2009, Kidney Disease: Improving Global Outcomes (KDIGO) initiated a collaborative meta-analysis and sponsored a controversies conference in October 2009 to examine the relationship of estimated glomerular filtration rate (eGFR) and albuminuria to mortality and kidney outcomes, which resulted in the CKD Prognosis Consortium. The CKD Prognosis Consortium published 4 meta-analysis papers addressing cardiovascular and renal outcomes and evaluating the definition and classification of the KDOQI classification. These meta-analyses were based on pooled data of 45 cohorts that included 1,555,332 participants from general, high-risk, and kidney disease populations. Given the considerable clinical and academic interest in the value of CKD in subpopulations such as elderly, diabetics, hypertensive individuals and potential differences in race and gender; the CKD Prognosis Consortium decided to continue their collaboration to evaluate these topics using data from the participating cohorts. In current, so called phase 2 analyses of the CKD Prognosis Consortium, interaction of CKD with age, race, gender, hypertension and diabetes will be evaluated. The CKD Prognosis Consortium is very well suitable for addressing these interactions as individual studies are underpowered to address these issues with reliable certainty.

5. Main Hypothesis/Study Questions:

The association of impaired eGFR and elevated albuminuria with both renal and cardiovascular outcomes will be similar by age, sex, race, hypertension and diabetes. In other words, there will be no effect modification or interaction of eGFR and albuminuria with age, sex, race, hypertension and diabetes. These comparisons will be conducted in the ARIC study which will then be meta-analyzed with other cohorts through the CKD-Prognosis Consortium.

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).

Data: Exposure Variables from ARIC visit 4:
- eGFR (serum creatinine). eGFR will be assessed by CKD-EPI epi equation.11
- Albuminuria (urinary albumin-to-creatinine ratio). Albuminuria will be expressed as urinary albumin-to-creatinine ratio (ACR).
**Interacting/Confounding Variables from ARIC visit 4 or closest exam:**
- Age, sex, race, hypertension, diabetes.
- Other established cardiovascular risk factors: history of cardiovascular disease (myocardial infarction, bypass grafting, percutaneous coronary intervention, heart failure or stroke), dummy variable hypercholesterolemia, cholesterol levels (total, HDL, LDL), triglycerides, diabetes mellitus, glucose levels with fasting status, smoking (current, former, never), BMI (height, weight), systolic blood pressure, diastolic blood pressure.
- Interfering medication (blood pressure including ACE inhibitors /ARB, Statins, as well as glucose lowering medication).

**Outcome Variables:**
- All cause mortality + Follow-up time.
- Cardiovascular mortality (death from myocardial infarction, sudden cardiac death, heart failure, stroke) + Follow-up time
- End-stage renal disease (initiation of dialysis, kidney transplantation, death coded due to kidney disease) + Follow-up time
- Acute kidney injury (Acute initiation of dialysis or ICD-9 code 584) + follow-up time
- Progression of CKD (an average annual decline in eGFR during follow-up of at least 2.5 ml/min/1.73m$^2$ per year and a last eGFR value being less than 45 ml/min/1.73m$^2$)

**Analysis plan and methods:**
Various cohorts from North America, Europe, Asia, and Australia will be pooled on individual participant level. Both continuous and categorical representations of eGFR and albuminuria will be explored, using Cox proportional hazards models. In predicting both renal and cardiovascular outcomes, interaction of albuminuria and eGFR with age, sex, race, hypertension and diabetes will be assessed.

**A.** First, we will use categorical analysis, with CKD being defined according to the clinically relevant categories that were evaluated in the phase 1 meta-analysis of the CKD-PC collaboration:
- eGFR > 105
- eGFR 90–105 (reference category)
- eGFR 75–90
- eGFR 60–75
- eGFR 45–60
- eGFR 30–45
- eGFR 15–30
- eGFR <15, because the expected number of subjects in this category will probably very low, these individuals might be excluded from the analysis.

The association of eGFR and albuminuria with renal and cardiovascular endpoints will be reported according to age categories (eg, less than 65 years of age vs more than 65 years of age), gender and race. Similarly the association of eGFR and albuminuria with renal and cardiovascular outcomes will be reported in hypertensive versus non-hypertensive and diabetic versus non-diabetic subjects.
B. We will evaluate the continuous association of eGFR and albuminuria with incidence rates of renal and cardiovascular outcomes using Cox proportional hazard models incorporating spline terms for eGFR with knots at 45, 60, 75, 90 and 105 mL/min/1.73 m² and albuminuria with knots at 10, 30, 300mg/g with and without adjustment for age, sex, race and other atherosclerosis risk factors. These will be presented according to age categories, gender, race, and hypertension and diabetes status.

C. Potential effect modification by age, gender, race, hypertension, and diabetes will be evaluated by formally meta-analyzing statistics indicating the difference in hazard ratios across subgroups (e.g., beta for interaction term). Dr. Woodward, the CKD-PC senior biostatistician, has worked with our analysis team and programmers to implement methods to test for interaction for specific points as well as the whole dose-response association within each study and meta-analyzed across studies.

Summary/conclusion:
By pooling various cohorts, from all over the world, on individual participant level; we will be able to address any interactions of eGFR and albuminuria with other cardiovascular risk factors, including age, sex, race, hypertension and diabetes. These results will serve as key work for future guidelines and patient care.

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.cscu.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)?

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.

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

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

These would be most relevant proposals. The key authors of each proposal are also 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.cscn.unc.edu/aric/forms/

11. 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.

References:

5. CP Wen, TYD Cheng and MK Tsai et al., All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan, Lancet 2008; 371;2173–2182.


