1.a. Full Title: Albuminuria and Kidney Function as Predictors of Cardiovascular Events and Mortality

b. Abbreviated Title (Length 26 characters): Albuminuria and CVD Events

2. Writing Group:
   Writing group members: Brad Astor (lead), Josef Coresh, Michael Steffes, Ron Hoogeveen, Tibor Fulop

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. BA

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3. Timeline:

This proposal will use available data. Analyses and manuscript preparation will be performed over the next six months.

4. Rationale:

Leakage of protein in the urine is a sensitive indicator of early kidney damage, especially in persons with diabetes. The prevalence and severity of albuminuria increase with lower GFR, and are significantly higher at each stage among individuals with diabetes. National Kidney Foundation (NKF) clinical practice guidelines define microalbuminuria, based on a random spot urine sample, as albumin:creatinine ratio (ACR) >30 mg/g, and macroalbuminuria as ACR >300 mg/g. The presence of albuminuria is one of the strongest predictors of progression of kidney disease, and is associated with a higher risk of cardiovascular disease and mortality in both diabetic and non-diabetic individuals. The Heart Outcomes Prevention Evaluation (HOPE) Study found a two-fold higher risk of mortality and cardiovascular events among diabetics with compared to without microalbuminuria. In the PREVEND Study of over 40,000 participants in a community-based study in The Netherlands, even the lowest measured level of urinary albumin (well below current clinical practice thresholds) was associated with a higher risk of cardiovascular and non-cardiovascular mortality.
The reasons for the increased risk of cardiovascular disease in subjects with albuminuria have not been well defined. Persons with albuminuria have a higher prevalence of other cardiovascular risk factors, including dyslipidemia, hypertension, and inflammatory markers. Adjustment for these other risk factors in large observational studies, however, does not substantially diminish the observed associations of albuminuria with cardiovascular disease. In addition, albuminuria is an indicator of systemic endothelial damage and may indicate greater vascular permeability or abnormalities in the endothelial-related components of the coagulation or fibrinolytic systems. It is unclear, however, whether albuminuria is simply a marker of endothelial damage or whether leakage of albumin into the renal tubules has more directly toxic effects.

The combined impact of decreased kidney function and albuminuria has not been well studied. A recent editorial in the New England Journal of Medicine stated, “Cohort studies that measure both urinary albumin excretion and estimated GFR and assess their combined associations with the risk of various outcomes are needed.” The proposed manuscript will specifically address this issue in the ARIC Study population.

5. Main Hypothesis/Study Questions:

Estimated kidney function (eGFR < 60 ml/min/1.73m²) and albuminuria (even if minimal) predict subsequent CVD, CHD, hospitalization and mortality, independent of other risk factors. The risk relationships with greater severity of kidney dysfunction and albuminuria will be quantified in this bi-racial general population sample of middle-aged and older adults.

6. Data (variables, time window, source, inclusions/exclusions):

All analyses will be performed locally by Dr. Astor, using available data. Urinary albumin, urinary creatinine and serum creatinine were measured in all participants at Visit 4. Participants with missing values for these variables or with severely decreased kidney function (<15 ml/min/1.73m²) will be excluded from analyses. Serum creatinine was measured using a modified kinetic Jaffe method. Serum creatinine concentration will be corrected for inter-laboratory differences and calibrated with Cleveland Clinic measurement standards. Estimated GFR will be calculated based on serum creatinine, age, race and sex using the abbreviated MDRD formula as we have done previously. Urinary albumin:creatinine ratio also will be calculated and analyzed using clinical cutoff (microalbuminuria 30-300 mg/g, macroalbuminuria 300+ mg/g) and as a continuous variable (including levels below the cutoff for microalbuminuria). These variables will be used to predict subsequent CHD events and mortality. An important component of the analyses will be an attempt to define the risk of CHD events across the entire range of ACR and eGFR. The latter analysis will use nonlinear models. In particular, we hypothesize that the relationship between eGFR and CHD will be stronger among individuals with some albuminuria.

Additional variables required for analyses include demographic factors (age, race, sex, center), comorbid conditions (blood pressure, diabetes status, prior CHD events), anthropometric data (waist circumference, waist:hip ratio, BMI), smoking status, alcohol intake, medication use (antihypertensives, lipid-lowering medications), and laboratory
variables (lipids, blood glucose, insulin). Participants with severely decreased kidney function (eGFR<15 ml/min/1.73 m²) will be excluded.

7.a. Will the data be used for non-CVD analysis in this manuscript? _ Yes _ No

    b. If Yes, is the author aware that the file ICTDER02 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

8.a. Will the DNA data be used in this manuscript? _____ Yes _____ No

    b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 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 _ 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)?

    #1012 “Association between cardiovascular risk and albuminuria in the ARIC Study,” proposed cross-sectional analyses between albuminuria and CVD risk factors.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _____ Yes _____ No

    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)* __________)

12. 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.
Reference List


