1.a. Full Title: Progression of CKD focusing on kidney function

b. Abbreviated Title (Length 26 characters): CKD progression & ESRD

2. Writing Group:
   Writing group members: Josef Coresh, Kunihiro Matsushita, Yingying Sang, Mark Woodward, Morgan Grams, Shoshana Ballew, and others for the CKD Prognosis Consortium

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
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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:
The progression of chronic kidney disease (CKD) is often slow, and until the stage of kidney failure, it is often asymptomatic, making difficult to incorporate kidney outcomes in clinical trials and thus hampering an efficient evaluation of drug effects on kidney function. In this context, the FDA accepts, a sufficiently large change serum creatinine
level (its doubling = 57% decline in estimated GFR [eGFR]) as a surrogate end point for kidney failure in clinical trials because it represents a marked loss of kidney function and is expected to be highly predictive of the development of kidney failure. However, a doubling of serum creatinine is generally a late event in CKD and takes a long time to develop, thus there is great interest in considering alternative endpoints for clinical trials to shorten the duration of trials and extend their application to earlier stages of CKD, but there is uncertainty about the associations of lesser declines in GFR with subsequent kidney failure. We will evaluate the impact of broad spectrum of change in eGFR (including lesser declines) on risk of end-stage renal disease beyond baseline first eGFR in the cohort joining the CKD Prognosis Consortium, including ARIC. The results will inform a large project sponsored by FDA and National Kidney Foundation and will be combined with the analyses involving randomized clinical trials and simulation studies in order to provide a rigorous examination of the research aim. We will also explore this association from clinical perspective, namely whether eGFR change in the past grants prognostic information beyond current (lastly measured) eGFR at a given time point.

5. Main Hypothesis/Study Questions:
To evaluate the impact of change in eGFR on subsequent clinical risk beyond baseline eGFR with implications for potential surrogate kidney outcomes in clinical trials to evaluate treatment effects on kidney function and prognostic information in clinical practice.

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 visits 1, 2, or 4:
- eGFR (serum creatinine). eGFR will be assessed by CKD-EPI epi equation.¹
- Albuminuria (urinary albumin-to-creatinine ratio). Albuminuria will be expressed as urinary albumin-to-creatinine ratio (ACR).
- Age, sex, race
- Other established cardiovascular risk factors: hypertension, diabetes, history of cardiovascular disease (myocardial infarction, bypass grafting, percutaneous coronary intervention, heart failure or stroke), dummy variable hypercholesterolemia, cholesterol levels (total, HDL, LDL), triglycerides, glucose levels with fasting status, smoking (current, former, never), BMI (height, weight), systolic blood pressure, diastolic blood pressure at baseline and during follow-up.
- Interfering medication (blood pressure including ACE inhibitors /ARB, Statins, as well as glucose lowering medication).

Outcome Variables:
- 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
Analysis Plan:
We will set a baseline period of interest (3 or 9 years in ARIC) and then a window for capturing the follow-up creatinine measures (±0.5 year of baseline period of interest [2.5 to 3.5 for 3-year window]). We will identify the closest creatinine measurement to the 3 year mark and then calculate the change (absolute change, % change, or slope) using available creatinine measurements. Then, this change will be linked to risk of future outcomes. We will exclude cases with no creatinine measurements in the window, those with events before the window, and those who have an eGFR <15 at baseline. The adjustment for covariates will be done separately for covariates measured at beginning or end of baseline period, as previously described. The statistics of interest would include hazard ratio according to change in eGFR and risk prediction statistics such as c-statistics and net reclassification improvement.

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 list under the Study Members Area of the web site at:  http://www.cscs.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)?
1395 - Change in kidney function and coronary heart disease, stroke, and all-cause mortality: The Atherosclerosis Risk in Communities (ARIC) Study; Matsushita, K.

1944 – Risk factors for AKI; Grams, M.

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.

References
