ARIC Manuscript Proposal #2517

PC Reviewed: 3/10/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Estimating lifetime risk of ESRD in the absence of donation

b. Abbreviated Title (Length 26 characters): **Lifetime risk of ESRD**

2. Writing Group:

Writing group members: Morgan Grams, Josef Coresh, Kunihiro Matsushita, Yingying Sang

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

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3. Timeline: Analysis will begin following proposal approval and, a manuscript will be completed within 6 months.

4. Rationale:

The practice of living kidney donation has gained widespread acceptance. Each year, 30,000 persons donate a kidney; in the US, 35% of all kidney transplants are from living donors.[1] However, information regarding the long-term health outcomes in living kidney donors is limited.[2] Although donor nephrectomy appears extremely safe in the short-term, there are little data on the long-term effects of the resultant single kidney status.[3] The most direct effect may be an increased risk of the donor developing ESRD. Thus,

transplant centers typically restrict kidney donation to persons at perceived extremely low risk of subsequent ESRD.[4]

Very little data exists to inform ESRD risk estimation in a low-risk population, and there is substantial variability in living donor evaluation and selection policies between transplant centers.[5, 6] In the recent European Best Practice Guideline group report, 10 of 24 statements regarding living donor selection criteria were left as "ungraded" due to lack of evidence.[7] Certain risk characteristics are particularly controversial, including the presence of hypertension, impaired glucose tolerance, hyperlipidemia, and obesity in kidney donor candidates. There has also been criticism of the common transplant center practice of employing universal selection criteria, irrespective of age and race.[2] Indeed, recent policy statements have advised caution in selecting younger donors and those of non-white race.[7]

With the goal of providing population-based evidence for living donor evaluation and selection guidelines, we estimated the lifetime incidence of ESRD in the absence of kidney donation in a relatively low-risk, nationally representative population. Pre-donation characteristics of particular interest included age, race, and sex, as well as lower eGFR levels, higher albuminuria, anti-hypertensive medication use and blood pressure, non-insulin dependent diabetes, obesity, dyslipidemia, and smoking status. Results of these analyses were used to develop a simplified risk calculator that could be used by transplant centers in the evaluation of potential kidney donors.

5. Main Hypothesis/Study Questions:
1-To estimate the lifetime risk of ESRD in a low-risk population according to individual risk characteristics, including age, race, sex, eGFR, albuminuria, blood pressure, anti-hypertensive medication use, obesity, smoking status, diabetes.

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 white and black ARIC participants with data on eGFR and systolic blood pressure (SBP)

Exclusions:
- Race other than white or black
- Missing data on eGFR or SBP

Exposures (independent variables):
- eGFR (linear splines, knot at 60, 90, 120 ml/min/1.73 m2)
- Systolic blood pressure
- Anti-hypertensive medication use
- Diabetes status (excludes those requiring insulin)
- Body mass index (linear spline, knot at 30 kg/m^2)

- Dyslipidemia (Total cholesterol and LDL cholesterol)
- Smoking (past and current)
- Albuminuria (log-transformed)

Outcome (dependent variables):

Incident ESRD was defined as initiation of dialysis therapy, transplantation, or death due to kidney disease. Cases with dialysis therapy and transplantation were identified by linkage to the US Renal Data System (USRDS), which captures information about all Americans who receive renal replacement therapy or are awaiting kidney transplantation.[8] Participants who were free of ESRD by December 31, 2010, were administratively censored.

Other variables of interest and covariates:

-Socio-demographics: age, sex, race

Statistical Analysis Plan:

Study Populations

The study population used to estimate the age-, sex-, and race-specific prevalence of comorbidities will be the National Health and Nutrition Examination Survey (NHANES) Third Survey (1988-1994) and continuous NHANES (1999-2010), a stratified probability sample of civilian, non-institutionalized persons in the United States. We will partition the population into lower risk and higher risk subgroups, with the latter defined by the presence of one or more severe comorbidities: eGFR <45 ml/min/1.73 m2, insulin-dependent diabetes, the use of 4 or more antihypertensive medications, systolic blood pressure >160/90 on medication or >170/100 off medication, urine albumin-to-creatinine ratio (ACR) >300 mg/g, or a history of coronary heart disease, stroke, congestive heart failure, or peripheral arterial disease.

The study population used to estimate risk factor associations with ESRD will include the lower risk subgroup of NHANES as well as the lower risk subgroup of 6 additional general population cohorts, including the Atherosclerosis Risk in Communities Study. Study data were obtained by the Chronic Kidney Disease Prognosis consortium for meta-analysis as previously described. Cohorts were eligible for inclusion in the consortium if they had available baseline measures of eGFR and albuminuria; for the current study, cohorts were required to have at least 15 ESRD events in the lower risk population. If a study did not have sufficient information to assess a particular variable used in exclusion, more conservative exclusion criteria were used. For example, if a cohort did not have information on insulin use, all diabetics were excluded. For the administrative cohorts, if there was no urine ACR available, it was assumed to be <300 mg/g.

Overall Estimates of the Lifetime Incidence of ESRD

The overall lifetime incidence of ESRD within groups of age, sex, and race in the US was estimated previously using data from the United States Renal Data System, a national registry of ESRD patients, and the US Census. We will partition the lifetime incidence of ESRD into the lower risk and higher risk populations in the following manner. Cox proportional hazards models (covariates: age, sex, race, lower-risk status, as well as

product terms between age and race, and lower-risk status and each demographic variable) will be fit in the full population of NHANES as well as 3 general population cohorts with full information on the variables used in exclusion criteria (including ARIC). The proportion of the ESRD risk in the lower risk population will be estimated as the inverse of the sum of the prevalence of higher risk status and the product term of risk ratio associated with lower-risk status and prevalence of lower risk status (e.g., 1/[risk $\text{ratio}_{\text{lower-risk}}$*$\text{prevalence}_{\text{lower-risk}}$ + $\text{prevalence}_{\text{higher-risk}}$]).

Estimating Lifetime Incidence of ESRD in the Presence of Risk Factors
Using the lower risk populations of the 7 cohorts, relative risks for ESRD will be estimated using multivariable Cox proportional hazards models for eGFR, albuminuria, smoking status, body-mass index, non-insulin dependent diabetes status, systolic blood pressure, and anti-hypertensive medication use, with adjustment for age (knot at 75 years), black race, age-race interaction, and sex as well. Models will be fit in each cohort individually and then combined using random effects meta-analysis. The meta-analyzed coefficients will be used to calculate a linear function for each participant in the lower-risk subgroup of NHANES as well as a set of average linear functions calculated using variable means within subgroups of age (10-year increments), sex, and race (white and black). The individual linear functions were then corrected for the average linear function in the corresponding subgroup, exponentiated, and inserted in the lifetime incidence estimate. The developed equation will estimate lifetime risk of ESRD given a set of individual risk factors and be published online.

Limitations:

Lifetime risk is estimated, not observed, and predicated on several assumptions:
-the proportion of ESRD events in the lower risk population is specified correctly
-the hazard ratio estimated through meta-analysis approximates the relative risk associated with a particular risk factor of interest
-the prevalence of comorbidities has been fairly constant over time

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 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)?

#203: Risk factors for decreased renal function in the ARIC study
#2370: Risk factors associated with eGFR trajectories in the ARIC study

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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