

## ARIC Manuscript Proposal # 1395

PC Reviewed: 08/12/08  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Change in kidney function and coronary heart disease, stroke, and all-cause mortality: The Atherosclerosis Risk in Communities (ARIC) Study

**b. Abbreviated Title (Length 26 characters):** change in kidney function & CVD

### 2. Writing Group:

Writing group members:

Kunihiro Matsushita, MD, PhD; Elizabeth Selvin, PhD, MPH; Lori D. Bash, MPH; Brad Astor, PhD, MPH; Josef Coresh, MD, PhD; others welcome.

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]

**First author:** Kunihiro Matsushita, MD, PhD  
**Address:** Department of Epidemiology  
Johns Hopkins Bloomberg School of Public Health  
Welch Center for Prevention, Epidemiology, and Clinical Research  
2024 E Monument Street, 2-600  
Phone: (410)502-2051 Fax: (410)955-0476  
E-mail: kmatsush@jhsph.edu

**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).

**Name:** Elizabeth Selvin PhD, MPH  
**Address:** Department of Epidemiology  
Johns Hopkins Bloomberg School of Public Health  
Welch Center for Prevention, Epidemiology, and Clinical Research  
2024 E Monument Street, 2-600  
Phone: (410) 614-3752 Fax: (410)955-0476  
E-mail: lselvin@jhsph.edu

### 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:

Numerous articles have reported that impaired kidney function, e.g., reduced glomerular filtration rate (GFR) or albuminuria, is a predictor of incident cardiovascular disease (CVD) [1-19]. Consequently, individuals with chronic kidney disease are placed in the highest risk group in CVD treatment guidelines [20,21].

Although most previous studies have investigated an association of a baseline kidney function to the incidence of CVD [1-16], a few studies in select populations report that sequential changes in kidney function, i.e., an increase in albuminuria or serum creatinine level, predicted incident CVD better than a single baseline measurement [17,18]. However, the literature investigating an association of changes in kidney function with future incidence of CVD in a general population is sparse.

If changes in kidney function provide prognostic information beyond a simple baseline assessment in a general population, the evaluation of changes in kidney function may be useful for risk stratification within the states defined by the conventional GFR estimation and currently used in clinical practice.

The ARIC Study provides an excellent opportunity to investigate a possible relationship between changes in kidney function and the incidence of CVD in a middle-aged, biracial population.

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

Hypothesis: Deterioration of kidney function (estimated GFR) will be associated with incident coronary heart disease (CHD), stroke, and all-cause mortality across categories of baseline GFR independently of traditional risk factors for CVD.

## **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 black and white ARIC subjects with measured serum creatinine, age, gender, and race allowing estimation of GFR.

### Exclusions:

Ethnicity other than black or white

Individuals without data required to estimate GFR

### Exposure: Change in Kidney Function

Kidney function will be estimated using the simplified version of the Modification of Diet in Renal Disease (MDRD) equation incorporating data of serum creatinine concentration, age, gender, and race from visit 1, 2, and 4 and measured in ml/min/1.73m<sup>2</sup>.

As an index of change in kidney function, we will use an annual rate of decline in estimated GFR (ml/min/1.73m<sup>2</sup>/year) from visit 1 to visit 2 or from visit 1 to visit 4 calculated as follows: (GFR at visit 2 – GFR at visit 1)/ [(v2date-v1date)/365.25] or (GFR at visit 4 – GFR at visit 1)/ [(v4date-v1date)/365.25], respectively.

### Outcome:

Incident CHD including a hospitalized myocardial infarction (MI), fatal CHD, cardiac procedure or electrocardiogram MI (serial changes), stroke, and all-cause death through

2004

Other variables of interest and covariates:

Sociodemographics: age, race, gender, education

Physical information: blood pressure, body mass index

Lifestyle: smoking status and alcohol consumption

Comorbidities: hypertension, diabetes, dyslipidemia, history of CVD

Statistical Analysis Plan:

Since those with higher estimated GFR showed greater annual declines in GFR than those with lower estimated GFR in a preliminary analysis, all analyses will be conducted after stratifying subjects according to baseline GFR level (visit 1) as proposed by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) [20], e.g., GFR <60, 60 to 89,  $\geq 90$  ml/min/1.73m<sup>2</sup>.

The primary analysis will use Cox proportional hazards models to estimate the association between declining rates of estimated GFR and incident CVD and all-cause mortality. We will adjust for the covariates listed above and also for the mean GFR of the baseline and second visit (analogous to the Bland-Altman approach).

An association between declining rate of GFR and outcomes might not be linear, since increase in GFR may result from reduced muscle mass related to some unhealthy condition. Therefore, the rate of decline in GFR will be mainly treated as a categorical variable according to its quartile, though analyses treating the rate of decline in GFR as a continuous variable will be also conducted.

Since there are only 372 (2.6%) subjects with GFR at visit 1 <60 among 14056 eligible having creatinine data at both visit 1 and 2, we may add 326 subjects with GFR between 45 and 59 to a group with GFR between 60 and 89. This modification seems to be justified because among moderate chronic kidney disease (GFR between 30 and 59), individuals with GFR between 45 and 59 are more frequent and there is controversy about whether they should be treated as high risk or as close to the normal range [15,16].

We will conduct a few subgroup analyses stratifying subjects according to race, gender, and prevalent CVD (yes/no), since there are articles showing that effects of CKD on incident CHD might differ between race, gender, and de novo/recurrent CHD [4,5,8].

Limitations:

The MDRD formula has been shown to underestimate systematically GFR in healthy individuals by much as 29% [6]. However, when used to calculate differences in kidney function within person, we believe that this formula is useful to estimate degree and direction of changes in kidney function. If an improved estimating equation is developed (likely by the CKD-EPI collaboration) we will use it.

Also, random fluctuation in creatinine levels over time would tend to increase the variance in our data. However, such random variation would most likely bias our findings toward a null result and lead to an underestimation of the true association.

Despite rigorous measurement of important covariates in the ARIC Study, we will also not be able to eliminate the possibility of residual confounding. And while additional measurements of serum creatinine would be useful to more fully characterize the slope of change, we are limited to those kidney function assessments conducted at the time of the ARIC examinations. Nonetheless, these data reflect a realistic clinical scenario with measurements assessed several years apart.

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 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  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

8.c. If yes, is the author aware that the participants with RES\_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?  
 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.csc.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)?

#172: Levels of Albumin, Creatinine, and Incident Coronary Heart Disease; Heiss, G

#758: Serum creatinine and risk of CVD: Atherosclerosis Risk in Communities (ARIC) Study; Ibrahim H

#952: Kidney function and anemia as risk factors for coronary heart disease and mortality: The ARIC Study; Astor, BC

#1028: Cardiovascular risk among adults with chronic kidney disease, with or without prior myocardial infarction; Wattanakit, K

#1058: Kidney Function and Risk of Peripheral Arterial Disease: Results from the Atherosclerosis Risk in Communities (ARIC) Study; Wattanakit, K

#1118: Reduced Kidney Function as a risk factor for incident heart failure: The ARIC Study; Kottgen, A

#1244: Kidney Dysfunction and Sudden Cardiac Death among Participants in the ARIC Study; Deo, R

#1348: Chronic kidney disease and risk of hospitalization: The Atherosclerosis Risk in Communities Study; Bash, LD



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17. Yuyun MF, Dinneen SF, Edwards OM, Wood E, Wareham NJ. Absolute level and rate of change of albuminuria over 1 year independently predict mortality and cardiovascular events in patients with diabetic nephropathy. *Diabet Med.* 2003;20:277-282.
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20. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39( Suppl 1):S1-266.
21. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culeton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on

Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*. 2003;108:2154-2169.