

ARIC Manuscript Proposal # 1754

PC Reviewed: 2/8/11
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Association of estimated glomerular filtration rate and albuminuria with ischemic and hemorrhagic strokes.

b. Abbreviated Title (Length 26 characters):

2. Writing Group:

Writing group members: Bakhtawar K. Mahmoodi, Kunihiro Matsushita, Brad C. Astor, Ron T. Gansevoort, Josef Coresh.

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

Chronic kidney disease (CKD) is a known independent risk factor for cardiovascular morbidity and mortality.¹ Studies on cardiovascular morbidity and mortality in CKD subjects generally report a composite cardiovascular endpoint without consideration of any potential risk differences among the subtypes of cardiovascular disease (i.e., coronary heart disease, stroke and cardiovascular mortality). Especially, the association of CKD with different subtypes of stroke (i.e. hemorrhagic versus ischemic) may vary that also seems plausible from pathophysiological point of view.² Thus far, however, only few studies addressed the association of CKD with subtypes of stroke.³⁻⁵ Major drawbacks of these studies are the limited number of hemorrhagic strokes and the use of the MDRD³ or Cockcroft-Gault⁴ equations for estimating glomerular filtration rate (eGFR) that are considered inferior to the newly available eGFR estimation equations.^{6,7} Moreover, while urinary albumin excretion is a requisite for defining stage 1 and stage 2 CKD,⁸ the study by Bos *et al*⁴ had no data on albuminuria, the study by Di Angelantonio *et al*⁵ had only dipstick measured albuminuria and the study by Aguilar *et al*³ was limited to subjects above 65 years of age.

Since, in epidemiological research in CKD subjects, ischemic and hemorrhagic strokes are usually pooled as one outcome measure, further research is warranted to assess whether these two potentially different phenotypes of stroke are equally associated with the two markers of CKD (i.e., eGFR and albuminuria). In this context it is relevant to evaluate various creatinine and cystatin C based eGFR equations,^{6,7} as well as albuminuria on continuous scale instead of semi-quantitative dipstick measurements. To overcome the problem of low numbers of hemorrhagic stroke, the ARIC study will be pooled with a comparable population-based prospective Dutch cohort (PREVEND study) on individual participant level. Approval for pooling from the PREVEND study PI (Dr Gansevoort) has already been obtained.

Several ARIC manuscript proposals (list manuscript proposal #) and published articles have investigated the association of eGFR and albuminuria with other types of atherosclerotic cardiovascular diseases such as coronary heart disease, heart failure, or peripheral artery disease.⁹⁻¹² This would allow us to compare the strength of the association of eGFR and albuminuria with stroke and other types of cardiovascular disease.

5. Main Hypothesis/Study Questions:

Different components defining CKD may be differently related to hemorrhagic versus ischemic stroke.

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).

Study Design:

The analysis will be prospective with coronary heart disease, ischemic stroke and hemorrhagic stroke serving as the outcome of interest. It is likely that the number of hemorrhagic strokes will be insufficient for appropriate analysis. Therefore, the ARIC study will be pooled on individual subject level data with a comparable population-based prospective Dutch cohort (PREVEND study). Approval for pooling has already been provided by the PREVEND primary investigator (Dr. RT Gansevoort).

Exclusion Criteria:

Participants with end-stage renal disease at baseline will be excluded.

Exposure Variables:

- Albuminuria (urinary albumin-to-creatinine ratio).

Albuminuria will be expressed as urinary albumin-to-creatinine ratio (ACR).

- eGFR (serum creatinine, serum cystatin C).

eGFR will be assessed by various estimation equations (i.e., creatinine based [MDRD, CKD-EPI] and cystatin C based).^{6,7} Since albuminuria was only measured during the 4th visit of ARIC, the 4th visit measurement of ARIC and baseline measurements of PREVEND will serve as the overall baseline.

Confounding/Interacting Variables:

- Age, sex, race

- Established CV risk factors: cholesterol, diabetes mellitus, glucose (in combination with fasting status), smoking, BMI, cardiovascular disease history, systolic blood pressure,

- Interfering medication (blood pressure, cholesterol, glucose lowering medication, as well as antiplatelet / antithrombotic agents).

- Study (ARIC versus PREVEND being entered as categorical variables)

Outcome Variables:

Incident ischemic and hemorrhagic stroke.

Data Analysis:

Distributions of pertinent variables will be reported, stratified by cohort (ARIC and PREVEND). The primary analysis will use Cox proportional hazards models. Both continuous and categorical representations of eGFR and albuminuria will be explored.

A. First, we will use categorical analysis, with CKD being defined according to the K/DOQI guidelines:

- No chronic kidney disease (CKD) and eGFR ≥ 90 (reference category)
- No CKD and eGFR 60-89
- CKD stage 1 (i.e., albuminuria $\geq 30\text{mg/d}$ and eGFR ≥ 90)
- CKD stage 2 (i.e., albuminuria $\geq 30\text{mg/d}$ and eGFR 60-89)
- CKD stage 3 without albuminuria (i.e., eGFR 30-59 and albuminuria $< 30\text{mg/d}$)
- CKD stage 3 with albuminuria (i.e., eGFR 30-59 and albuminuria $> 30\text{mg/d}$)

For stage 4 there are probably very few subjects for separate analysis (e.g. in PREVEND only 8 subjects have CKD stage 4)

B. Second, in another Cox regression analysis eGFR and albuminuria will be expressed as continuous variables. The risk on continuous scale of eGFR and albuminuria will be visually represented by linear spline models using the same cut-off values for knots as presented in the paper by Matsushita et al.¹

- We will check whether there is an interaction between albuminuria and eGFR in predicting different subtypes of stroke.
- In case there is an interaction, the risk of GFR for that particular subtype of cardiovascular disease will be assessed in various albuminuria strata.
- In case there is no interaction, both variables will be implemented in the same model.

Adjustment:

For analyses A and B the following models will be run:

- Crude
- Adjustment for age, race and gender
- Adjustment for age, race, gender, established CV risk factors and interfering medication.

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.csc.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)?

1. # 1423 Cystatin C-based estimated GFR and albuminuria as predictors of coronary heart disease (CHD) events and mortality; Astor B et al
2. # 1395 Change in kidney function and coronary heart disease, stroke, and allcause mortality. Matsushita K et al
3. # 1574 Comparison of novel markers of kidney function and prediction of cardiovascular events, mortality, and kidney failure. Astor B et al
4. # 1663 Risk Factors for Hemorrhagic Stroke II: A pooled study of CHS and ARIC. Folsom A et al.
5. #1028: Cardiovascular risk among adults with chronic kidney disease, with or without prior myocardial infarction; Wattanakit K et al
6. #1058: Kidney Function and Risk of Peripheral Arterial Disease: Results from the Atherosclerosis Risk in Communities (ARIC) Study; Wattanakit K et al
7. #1118: Reduced Kidney Function as a risk factor for incident heart failure: The ARIC Study; Kottgen A et al
8. # 1197 Albuminuria as a Predictor of Incident Heart Failure Hospitalization and Mortality in the Atherosclerosis Risk in Communities (ARIC) Study; Kottgen A et al.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ☐ Yes ☒ 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.csc.unc.edu/aric/forms/>

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.

References:

1. Matsushita K, van der Velde M, Astor BC et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073-81.
2. Ariesen MJ, Claus SP, Rinkel GJ et al. Risk factors for intracerebral hemorrhage in the general population: A systematic review. *Stroke*. 2003; 34:2060-2066

3. Aguilar MI, O'Meara ES, Seliger S et al. Albuminuria and the risk of incident stroke and stroke types in older adults. *Neurology*. 2010;75:1343–50.
4. Bos MJ, Koudstaal PJ, Hofman A, Breteler MM. Decreased glomerular filtration rate is a risk factor for hemorrhagic but not for ischemic stroke: the Rotterdam Study. *Stroke*. 2007;38:3127-32.
5. Di Angelantonio E, Chowdhury R, Sarwar N et al. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. *BMJ*. 2010;341:c4986.
6. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–12
7. Stevens LA, Coresh J, Schmid CH et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis*. 2008;51:395-406.
8. Levey AS, de Jong PE, Coresh J et al. The definition, classification and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*. 2010; (in press)
9. Perkovic V, Verdon C, Ninomiya T et al. The relationship between proteinuria and coronary risk: a systematic review and meta-analysis. *Plos Med*. 2008;5:e207.
10. Di Angelantonio E, Danesh J, Eiriksdottir G et al. Renal function and risk of coronary heart disease in general populations: new prospective study and systematic review. *PLoS Med*. 2007;4:e270.
11. Dhingra R, Gaziano JM, Djoussé L. Chronic Kidney Disease and the Risk of Heart Failure in Men. *Circ Heart Fail*. 2011 (in press)
12. Wu CK, Yang CY, Tsai CT et al. Association of low glomerular filtration rate and albuminuria with peripheral arterial disease: the National Health and Nutrition Examination Survey, 1999-2004. *Atherosclerosis*. 2010;209:230-4.