

ARIC Manuscript Proposal # 1653

PC Reviewed: 5/11/10
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: The association of glomerular filtration rate and albuminuria with incident hypertension: The Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters): Kidney indices & hypertension

2. Writing Group:

Writing group members: Kunihiro Matsushita, Brad Astor, Josef Coresh, 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]

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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:

Hypertension is one of the most prevalent risk factors for cardiovascular disease (CVD), affecting one-third of US adults.¹ Persons with hypertension have 5 years shorter total life expectancy and 7 years shorter CVD-free survival as compared to those without hypertension.¹ In 90 percent of persons with hypertension, a specific cause cannot be determined and, thus, they are diagnosed as primary (or essential) hypertension.²

Although, thus, essential hypertension is a multifactorial entity, various basic studies have suggested that kidney dysfunction may predate essential hypertension. Hypertension can be induced by subtle renal injury in rats.³ The number of nephrons is lower in some animal models with hypertension as compared to those without hypertension.⁴ Similarly, a small pathological study has reported that persons with essential hypertension have lower number of nephrons as compared to normotensive individuals.⁵

Several epidemiological studies have investigated the association of kidney dysfunction with incident hypertension.⁶⁻¹¹ Most of them⁶⁻⁹ have focused on albuminuria, a marker of kidney damage, and reported its positive association with incident hypertension. However, only two studies, to our knowledge, have investigated both glomerular filtration rate (GFR), the best overall integrating measure of kidney function, and albuminuria together regarding their associations with the development of hypertension,^{10, 11} with conflicting results. Brantsma and colleagues reported that estimated GFR (eGFR) may be only marginally associated with incident hypertension only when albuminuria is extremely low, while albuminuria is consistently associated with incident hypertension independently of potential confounders.¹⁰ In contrast, Kestenbaum and colleagues have shown that reduced eGFR, represented by elevated serum cystatin C concentrations, but not albuminuria, is associated with incident hypertension. However, since cystatin C is known to be regulated also by non-kidney factors.¹²

Using the ARIC study visit 4 data as a baseline provides an excellent opportunity to evaluate independent associations of eGFR and albuminuria with incident hypertension in a middle-aged, biracial population.

5. Main Hypothesis/Study Questions:

Hypothesis: eGFR and albuminuria are associated with incident hypertension independently of each other and other potential risk factors.

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 participants with data of serum creatinine and albuminuria at visit 4 (the only visit for which albuminuria data are available)

Exclusions:

- Ethnicity other than black or white
- Individuals without data of serum creatinine or albuminuria
- Prevalent hypertension cases

Prevalent hypertension at visit 4 will be defined as systolic blood pressure (SBP) of ≥ 140 mmHg, diastolic blood pressure (DBP) of ≥ 90 mmHg, a self-reported

physician diagnosis of hypertension, or medical treatment for hypertension at any visits (visit 1 through visit 4). Sensitivity analyses will also exclude individuals with (SBP) ≥ 120 mmHg or DBP ≥ 80 mmHg at any of the previous visits.

-Prevalent coronary heart disease (CHD) cases (treatment may affect blood pressure/kidney measures)

Prevalent CHD at visit 4 will be defined as self-reported CHD at visit 4 or adjudicated incidence of CHD between visit 1 and visit 4.

-Prevalent heart failure (HF) cases (treatment may affect blood pressure/kidney measures)

Prevalent HF will be defined as the Gothenburg criteria stage 3^{13, 14} at visit 4 or incident HF hospitalization between visit 1 and visit 4.

Exposure:

-eGFR

eGFR will be calculated using the recently proposed CKD-EPI equation¹⁵ incorporating data of serum creatinine concentration, age, gender, and race at visit 4 and measured in ml/min/1.73 m². We will also evaluate the consistency of our results by using eGFR incorporating age, gender, race, serum creatinine and cystatin C¹⁶ as well as more novel filtration markers (beta trace protein [BTP] and $\beta 2$ microglobulin [B2M]) measured in the ARIC-CKD ancillary study.

-albuminuria

As recommended in clinical guidelines,¹⁷ urine albumin-to-creatinine ratio (UACR) will be used as a measure of albuminuria.

Outcome:

-Incident hypertension:

We will use self-reported diagnosed hypertension and self-reported medications for hypertension from annual follow-up phone calls after visit 4 with most recent data available. We recognize the limitation of not having blood pressure measurements and hence missing undiagnosed hypertension but knowledge and diagnosis of hypertension, even among minority groups, is quite high.¹⁸

Other variables of interest and covariates:

Sociodemographics: age, race, gender, education, parental history of hypertension

Physical information: blood pressure, body mass index, presence/absence of left ventricular hypertrophy by electrocardiogram and carotid atherosclerosis by ultrasound

Lifestyle: smoking status and alcohol habit

Comorbidities: diabetes, dyslipidemia

Statistical Analysis Plan:

The primary analysis will use Cox proportional hazards models to quantify the association of eGFR and UACR with incident hypertension. Both kidney measures will be treated as categorical (quartiles and clinical categories) and continuous variables with splines respectively in the models. We will adjust for the covariates listed above. We will repeat the analysis after stratifying the study sample by gender and race. We will test interaction between eGFR and UACR on incident hypertension.

We will conduct a few sensitivity analyses. Firstly, since the adjustment for baseline blood pressure may bias the associations,¹⁹ we will also analyze models without blood pressure variables at baseline. Secondly, since CHD or HF events during follow-up can

act as competing endpoints, we will conduct the same analysis among participants who did not experience incident CHD or HF during follow-up. Thirdly, we will analyze a subpopulation who had normal blood pressure (<120/80 mmHg) at baseline (visit 4). Finally, by using eGFR data at visit 1 and incident hypertension by visit 4, which incorporates self-reported hypertension and blood pressure measurements, we will evaluate whether the association of eGFR with incident hypertension varies across definitions of incident hypertension (self reported vs. all hypertension including undiagnosed hypertension).

Limitations:

As with any observational study, we will not be able to rule out the possibility of residual confounding. There will be misclassification of incident hypertension by only using self-reported hypertension. However, self-reported incident hypertension has been used in previous studies,^{8,9} and we will also evaluate whether the inclusion of measured blood pressure would change the relative association of eGFR with hypertension using data from visit 1 to visit 4. We will also examine the consistency of self reported hypertension. A single measurement of UACR is an additional limitation.

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)?

The most related proposal is MP#1012 titled “Association between Cardiovascular Risk Factors and Albuminuria in the ARIC Study”, which focused on the influence of blood pressure on albuminuria (opposite direction of the current proposal).²⁰ The corresponding author is also involved in the current proposal. Other related proposals are listed below.

Proposals investigating the associations of eGFR and/or albuminuria with CVD

- #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
- # 1123: Albuminuria and Kidney Function as Predictors of Cardiovascular Events and Mortality; Astor, BC
- # 1197: Albuminuria as a Predictor of Incident Heart Failure Hospitalization and Mortality in the Atherosclerosis Risk in Communities (ARIC) Study; Kottgen, A
- #1244: Kidney Dysfunction and Sudden Cardiac Death among Participants in the ARIC Study; Deo, R
- # 1423: Cystatin C-based estimated GFR and albuminuria as predictors of coronary heart disease (CHD) events and mortality; Astor, BC

Proposals using incident hypertension as the primary outcome

- #270C: Relationship between postural change in blood pressure and three-year incidence of hypertension; Holme, I.
- #365: Women's Employment Status: Associations with Prevalent and Incident Hypertension; Rose, K.
- #416: Plasma Fatty Acid Composition and 6-Year Incidence of Hypertension in Middle-Aged Adults; Zheng, ZJ.
- #422: Physical Activity and Incidence of Hypertension in Men and Women; Pereira, MA.
- #423: Insulin and Hypertension; Folsom, AR.
- #424: Magnesium and Hypertension; Folsom, AR.
- #425: Fibrinogen and Hypertension; Folsom, AR.
- #429: Explaining the association between race and hypertension incidence; Nieto, J.
- #451: Alcohol consumption and incident hypertension; Fuchs, FD.
- #456: Neighborhood socioenvironmental characteristics, race, and incidence of hypertension in the ARIC cohort; Roux, AVD.
- #459: The relationship of physical activity to incident hypertension: The ARIC Study; Evenson, K.
- #776: Retinal arteriolar diameter and its relation to Incident Hypertension: The Atherosclerosis Risk in Communities Study; Wong, T.
- #998: The Natural History of Pre-Hypertension; Kshirsagar, AV.
- # 1032: C-Reactive Protein and the Change in Blood Pressure among Individuals Initially without Hypertension; Kshirsagar, AV.

7. Inoue T, Iseki K, Higashiuesato Y, Nagahama K, Matsuoka M, Iseki C, et al. Proteinuria as a Significant Determinant of Hypertension in a Normotensive Screened Cohort in Okinawa, Japan. *Hypertens Res* 2006; 29:687-93.
8. Wang TJ, Evans JC, Meigs JB, Rifai N, Fox CS, D'Agostino RB, et al. Low-Grade Albuminuria and the Risks of Hypertension and Blood Pressure Progression. *Circulation* 2005; 111:1370-6.
9. Wang TJ, Gona P, Larson MG, Levy D, Benjamin EJ, Tofler GH, et al. Multiple Biomarkers and the Risk of Incident Hypertension. *Hypertension* 2007; 49:432-8.
10. Brantsma AH, Bakker SJL, de Zeeuw D, de Jong PE, Gansevoort RT, for the PSG. Urinary Albumin Excretion as a Predictor of the Development of Hypertension in the General Population. *J Am Soc Nephrol* 2006; 17:331-5.
11. Kestenbaum B, Rudser KD, de Boer IH, Peralta CA, Fried LF, Shlipak MG, et al. Differences in Kidney Function and Incident Hypertension: The Multi-Ethnic Study of Atherosclerosis. *Annals of Internal Medicine* 2008; 148:501-8.
12. Knight EL, Verhave JC, Spiegelman D, Hillege HL, De Zeeuw D, Curhan GC, et al. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. *Kidney International* 2004; 65:1416-21.
13. Eriksson H, Caidaul K, Larsson B, Ohlson LO, Welin L, Wilhelmsen L, et al. Cardiac and pulmonary causes of dyspnoea--validation of a scoring test for clinical-epidemiological use: The Study of Men Born in 1913. *Eur Heart J* 1987; 8:1007-14.
14. Wilhelmsen L, Eriksson H, Svardsudd K, Caidahl K. Improving the detection and diagnosis of congestive heart failure. *Eur Heart J* 1989; 10 Suppl C:13-8.
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17. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; 39:S1-266.
18. Victor RG, Leonard D, Hess P, Bhat DG, Jones J, Vaeth PAC, et al. Factors Associated With Hypertension Awareness, Treatment, and Control in Dallas County, Texas. *Arch Intern Med* 2008; 168:1285-93.
19. Glymour MM, Weuve J, Berkman LF, Kawachi I, Robins JM. When is baseline adjustment useful in analyses of change? An example with education and cognitive change. *Am J Epidemiol* 2005; 162:267-78.
20. Hsu CC, Brancati FL, Astor BC, Kao WH, Steffes MW, Folsom AR, et al. Blood pressure, atherosclerosis, and albuminuria in 10 113 participants in the Atherosclerosis Risk In Communities study. *Journal of Hypertension* 2009; 27:397-409.