ARIC Manuscript Proposal # 1197

PC Reviewed: _10/_27_/06 **Status: __A___** **Priority: __2__**
SC Reviewed: _10/_27_/06 **Status: ___A__** **Priority: __2__**

1.a. Full Title: Albuminuria as a Predictor of Incident Heart Failure Hospitalization and Mortality in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Albuminuria and Heart Failure

2. Writing Group:
Writing group members: Anna Kottgen, Laura R. Loehr, Michael Steffes, Josef Coresh
Invited: Wayne D. Posamond, Charles C. Hsu

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

F**irst author**: Anna Kottgen

Address: Johns Hopkins University
2024 E. Monument St
Suite 2-602
Baltimore, MD 21287

Phone: (410) 245-6897 Fax: (410) 955-0476
E-mail: akottgen@jhsph.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author): Josef Coresh

Address: Johns Hopkins University
2024 E. Monument St
Suite 2-600
Baltimore, MD 21287

Phone: (410) 955-0495 Fax: (410) 955-0476
E-mail: coresh@jhu.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:

Heart failure (HF) has a prevalence of almost 5 million among the U.S. population and a yearly incidence rate of more than 500,000. Data from the Framingham Study suggests that the lifetime risk of heart failure is 1 out of 5 for both genders [1]. The prevalence, incidence, and number of deaths with HF as the underlying cause of death in the United States are increasing [2].

Albuminuria has consistently been reported to be associated with cardiovascular outcomes in both diabetic and non-diabetic individuals [3-5]. Albuminuria is defined as the excretion of albumin in the urine, and in its excessive state can be sub-classified as microalbuminuria (albumin excretion 30-299 mg/24h), and macroalbuminuria (albumin excretion ≥300 mg/24h) [6]. A urinary albumin-to-creatinine ratio (ACR) can be calculated from an untimed urine sample, such as a spot collection, which closely approximates the albumin excretion in a 24-hour urine sample [7]. Microalbuminuria is one of the earliest signs of chronic kidney disease (CKD). From a large population-based survey (National Health and Nutrition Examination Survey, NHANES III), it has been estimated that the prevalence of microalbuminuria in the general U.S. population lies between 8 and 11%, and affects about 29% of the diabetic and 16% of the hypertensive subpopulation [8, 9].

Regarding the specific association between albuminuria and heart failure, the Heart Outcomes Prevention Evaluation (HOPE) Study found a 3.5-fold higher risk of incident HF hospitalizations in diabetics within the highest quartile of ACR compared to diabetics within the lowest quartile of the ACR, and similar numbers for non-diabetic individuals [4].

The underlying mechanism of the association between albuminuria and HF needs further investigation. Albuminuria is associated with several cardiovascular risk factors that are known to cause or be associated with CHD, the most common cause of HF in the U.S. These factors include hypertension, hyperglycemia, smoking, infection, and renal dysfunction. Moreover, albuminuria might reflect a state of vascular and specifically endothelial dysfunction [10]. In addition, there is evidence that neurohumoral mechanisms contribute to the development of HF in individuals with albuminuria as a marker of kidney dysfunction [11]. It is still unclear whether direct toxic effects of albumin in the kidney contribute to this mechanism by leading to kidney damage, thereby inducing hormonal changes (e.g., of the rennin-angiotensin-aldosterone system) that might exert systemic effects.

The ARIC Study as a large community based study provides an excellent opportunity to investigate a possible relationship between levels of albuminuria and heart failure in a middle-aged, biracial population.

5. Main Hypothesis/Study Questions:

1. Higher levels of albuminuria (either micro- and macroalbuminuria or ACR ≥ 30 mg/g) will predict a higher incidence of heart failure hospitalizations and deaths over the course of follow-up.

2. The relationship above will be independent of other risk factors for heart failure including demographics, existing (baseline) or incident coronary heart disease, and coronary heart disease risk factors.

3. The relationship of albuminuria and incident HF will be present across categories of estimated glomerular filtrarion rate (eGFR), another marker of kidney function. We hypothesize that albuminuria will predict increased risk for incident HF even in individuals with normal levels of kidney function based on eGFR, although the relationship of albuminuria and incident HF will be graded across the categories of eGFR with the strongest association observed in the lowest category of eGFR.

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).

All analyses will be conducted locally by Anna Kottgen.

Main Exposure:

Albuminuria as measured by the urinary albumin-to-creatinine ratio (ACR). Urinary albumin, urinary creatinine and serum creatinine were measured in all ARIC participants at Visit 4 (n = 11,477) at the University of Minnesota (laboratory M. Steffes). Serum creatinine was measured using a modified kinetic Jaffe method.

Main outcome:

The main outcome will be the first HF hospitalization or HF as the underlying cause of death after study visit 4 (baseline of this analysis since this is the time the exposure variable was collected). HF cases are assessed from hospitalization records (hospital discharge diagnoses from cohort eligibility forms) and death certificates (ICD-9 code 428, ICD-10 code I50). Since visit 4 there have been 410 cases of incident HF hospitalizations or deaths.

Exclusions:

Participants with missing values for urinary albumin or creatinine will be excluded from analyses. In addition, individuals missing race, age, gender, or serum creatinine at visit 4 will be excluded from analyses, as it would not be possible to estimate the glomerular filtration rate (GFR), another important marker of kidney function.

Furthermore, individuals with evidence of prevalent HF at visit 4 as defined by the Gothenburg criteria, stage 3, or the self-reported current intake of HF medication will be excluded from analyses [12]. As full information regarding the individual criteria that are summed to obtain the Gothenburg score are only available for visit 1, individuals with prevalent HF at visit 1 as defined by the Gothenburg criteria, stage 3, will be excluded from analyses even if they do not meet the Gothenburg criteria at visit 4. In addition, those with an incident HF hospitalization before visit 4 will also be excluded. We will strive to keep the exclusion criteria due to prevalent HF consistent with those in the manuscript proposals 1118, 1125, and 1164.

Covariates:

Additional variables required for analyses include demographic factors (age, race, sex, education, study center), comorbid conditions (blood pressure, diabetes status, prevalent coronary heart disease (CHD) at visit 4 as well as incident CHD over the course of follow-up), anthropometric data (waist circumference, waist-to-hip ratio, BMI), smoking status, alcohol intake, medication use (antihypertensives, lipid-lowering medications), and laboratory measurements (serum creatinine, LDL and HDL cholesterol, hemoglobin, serum albumin, CRP). All covariates with the exception of the incident CHD variable and CRP will be taken from study visit 4. The estimated glomerular filtration rate (eGFR) will be calculated from age, sex, gender, and serum creatinine, using the re-expressed abbreviated MDRD Study equation [13] and will be incorporated as a covariate. Finally, variables providing information to calculate the Gothenburg score (cardiac and pulmonary characteristics, EKG, medication) will be taken from visit 4 if available and otherwise from visit 1.

Data analysis:

Individuals will be followed from baseline (visit 4) until the earliest of the following dates: date of the first HF hospitalization, HF death, loss to follow-up, or December 31st, 2002 (end of follow-up). Crude and age-adjusted HF incidence rates will be calculated using person-time methods.

Albuminuria will be analyzed categorically using clinical cutoffs (normoalbuminuria <30 mg/g, microalbuminuria 30-300 mg/g, macroalbuminuria 300+ mg/g) [6]and as a continuous variable (ACR), including levels below the cutoff for microalbuminuria. For sensitivity analyses, sex-specific cutoffs for micro- and macroalbuminuria will also be used.

Using Cox proportional hazards models, the relative hazard of incident HF will be modeled as a function of albuminuria at visit 4 (both categorically and continuously) as well as covariates. Models will be built subsequently incorporating these pre-specified covariates, and nested models will be tested for significance using likelihood ratio testing. The appropriateness of the proportional hazards assumption will be assessed visually by inspecting the complementary log(-log[survival function]) curves. An important component of the analyses will be an attempt to define the risk of HF across the entire range of the ACR. This analysis will incorporate the use of spline models to explore deviations from linearity. The relationship of albuminuria and HF will also be explored at different levels of eGFR (normal: eGFR $\geq$ 90 ml/min/1.73m^2, mildly reduced: eGFR 60-89 ml/min/1.73m^2, and moderately and severely reduced: eGFR < 60 ml/min/1.73m^2, in accordance with National guidelines [14].

Since albuminuria has also been shown to be a risk factor for incident CHD and CHD is the main cause of HF in the United States [15], analyses will be conducted stratified by the presence of prevalent CHD at visit 4. In addition, analyses for those without prevalent CHD at visit 4 will be conducted accounting for incident CHD over the course of follow-up by censoring individuals at the time of an incident CHD event (MI, fatal CHD, silent MI, or revascularization procedure).

Limitations:

The main limitation of this study is the use of a single urine sample to determine the level of the main exposure, albuminuria. Clinical recommendations define the presence of albuminuria above clinical cutoffs as the presence of these levels in at least two of three consecutive urine samples [16]. Since the level of albuminuria is subject to

high physiologic variation, the potential for misclassification of our main exposure exists. In order to address this issue, analyses will be repeated excluding participants that were pregnant, reported strenuous exercise (vigorous sports or exercise within the last 12 hours) for those who have this information available. Additionally, information about the persistence of microalbuminuria from another study (NHANES) with repeat measurements can help in modeling biologic and measurement variability to assess the effect on the association.

Another limitation pertains to misclassification of the outcome. Incident HF was not adjudicated by an adjudication committee. Moreover, information is only available for HF hospitalizations and deaths, and echocardiographic data are missing. The Gothenburg criteria used to exclude prevalent HF cases are reported to have high specificity but only moderate sensitivity [17], therefore, our exclusion of prevalent HF cases might have missed a few individuals.

Finally, our main exposure as well as many covariates might have changed over the course of follow-up.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?

MP 1123: Albuminuria and Kidney Function as Predictors of Cardiovascular Events and Mortality
MP 1118: Kidney function as a Risk Factor for Heart Failure Hospitalization: The Atherosclerosis Risk in Communities (ARIC) Study

MP 1012: Association between Cardiovascular Risk Factors and Albuminuria in the ARIC Study
MP 1125: Diabetes, obesity and insulin resistance as risk factors for incident hospitalized heart failure: The Atherosclerosis Risk in Communities (ARIC) Study
MP 1164: Hemoglobin A1c as a Risk Factor for Heart Failure Hospitalization among Persons with Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X_ Yes ____ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)
__X B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* ____2002.02_)

*ancillary studies are listed by number at http://www.cscc.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. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D, Framingham Heart Study. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation.* 2002; 106: 3068-3072.

2. *MMWR.* 1998; 47: 633-637.

3. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, de Jong PE, Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation.* 2002; 106: 1777-1782.

4. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S, HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA.* 2001; 286: 421-426.

5. Romundstad S, Holmen J, Hallan H, Kvenild K, Kruger O, Midthjell K. Microalbuminuria, cardiovascular disease and risk factors in a nondiabetic/nonhypertensive population. The Nord-Trondelag Health Study (HUNT, 1995-97), Norway. *J Intern Med.* 2002; 252: 164-172.

6. American Diabetes Association. Standards of Medical Care in Diabetes - 2006. *Diabetes Care.* 2006; 29: S4-S42.

7. Nathan DM, Rosenbaum C, Protasowicki VD. Single-void urine samples can be used to estimate quantitative microalbuminuria. *Diabetes Care.* 1987; 10: 414-418.

8. Jones CA, Francis ME, Eberhardt MS, Chavers B, Coresh J, Engelgau M, Kusek JW, Byrd-Holt D, Narayan KM, Herman WH, Jones CP, Salive M, Agodoa LY. Microalbuminuria in the US population: third National Health and Nutrition Examination Survey. *Am J Kidney Dis.* 2002; 39: 445-459.

9. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis.* 2003; 41: 1-12.

10. Schalkwijk CG, Stehouwer CD. Vascular complications in diabetes mellitus: the role of endothelial dysfunction. *Clin Sci (Lond).* 2005; 109: 143-159.

11. Sun Y. The renin-angiotensin-aldosterone system and vascular remodeling. *Congest Heart Fail.* 2002; 8: 11-16.

12. Eriksson H, Caidahl K, Larsson B, Ohlson LO, Welin L, Wilhelmsen L, Svardsudd K. 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: 1007-1014.

13. Hallan S, Astor B, Lydersen S. Estimating glomerular filtration rate in the general population: the second Health Survey of Nord-Trondelag (HUNT II). *Nephrol Dial Transplant.* 2006; 21: 1525-1533.

14. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002; 39: S1-266.

15. Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. *Circulation.* 1998; 97: 282-289.

16. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, Zeeuw D, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2005; 67: 2089-2100.

17. Fonseca C, Oliveira AG, Mota T, Matias F, Morais H, Costa C, Ceia F, EPICA Investigators. Evaluation of the performance and concordance of clinical questionnaires for the diagnosis of heart failure in primary care. *Eur J Heart Fail.* 2004; 6: 813-20, 821-2.