ARIC Manuscript Proposal #2654

PC Reviewed: 10/13/15   **Status: <u>A</u>**   **Priority: <u>2</u>**
SC Reviewed: _____   **Status:** _____   **Priority:** ____

1.a. Full Title:
Anemia, chronic kidney disease, and incident heart failure: The Atherosclerosis Risk in Communities (ARIC) Study.

   b. Abbreviated Title (Length 26 characters):
Anemia, CKD, and incident HF

2.   Writing Group:

Writing group members:
Junichi Ishigami, Morgan Grams, Rakhi Naik, Josef Coresh, Kunihiro Matsushita, others welcome

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

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3.   Timeline:

Data ascertainment for the present study has been already completed. Data analysis and manuscript preparation will be done in the next 6 months.

4. Rationale:

Heart failure (HF) is an important complication of chronic kidney disease (CKD). Indeed, HF is the most common cardiovascular subtype among patients on dialysis.[1] Even at milder stages, reduced estimated glomerular filtration rate (eGFR)[2] and elevated albuminuria[3] are independently associated with increased risk of incident HF. Causes responsible for the increased risk are multifactorial. Volume overload according to reduced kidney function is certainly important.[4] Also, capillary density in left ventricle is reduced in individuals with CKD,[5] limiting oxygen supply to the myocardium. In addition, vascular calcification and arterial stiffness are common in CKD individuals[6] and may result in ventricular-arterial coupling mismatch.

Anemia is another potential pathophysiological condition behind the link of CKD with HF. Various mechanisms including decreased synthesis of erythropoietin,[7] iron deficiency,[8] and chronic inflammation[9] contribute to the development of anemia in individuals with CKD. Anemia increases cardiac workload,[10] induces subsequent left ventricular hypertrophy,[11] and thus elevates the risk of HF. Indeed, anemia is a known risk factor of HF among older adults with decreased kidney function.[12] However, whether this synergistic contribution of anemia and kidney dysfunction to HF risk is generalizable to the general population is yet to be investigated, although interaction between anemia and kidney dysfunction is reported for coronary heart disease[13] and stroke.[14] These studies suggested that the excess risk of cardiovascular disease from anemia could be more evident in individuals with reduced kidney function.

Albuminuria, the other key element of CKD, and anemia also interact with each other. Anemia is a risk factor for incident albuminuria in type 2 diabetic individuals.[15] Mechanisms linking anemia to albuminuria are not fully understood, but chronic hypoxia,[16] and hyperfiltration with increased renal blood flow[17] could be related to the development of albuminuria. In a cross sectional study of type 2 diabetes, albuminuria and reduced eGFR are both associated with higher prevalence of anemia.[18] However, the pattern of anemia prevalence in the cross-categories of eGFR and albuminuria proposed in the new international CKD guidelines[19] has not been explicitly evaluated in a large sample. Moreover, to our knowledge, no study has investigated potential interaction between albuminuria and anemia in terms of HF risk.

Therefore, the aim of the study was first to examine prevalence of anemia across a wide range of levels of eGFR and albuminuria and second to explore the interaction between anemia and these CKD measures in terms of subsequent HF risk in a bi-ethnic community-based cohort, the Atherosclerosis Risk in Communities (ARIC) study.

5. Main Hypothesis/Study Questions:
   1. Both reduced eGFR and elevated albuminuria are independently associated with higher prevalence of anemia.
   2. Contribution of anemia to risk of incident heart failure is enhanced in those with reduced eGFR and elevated albuminuria.

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).

Inclusion criteria
  - All ARIC study participants whose serum creatinine, serum cystatin C, urine albumin-to-creatinine ratio (ACR), and serum hemoglobin levels were measured.
  - White and black race participants.

Exclusion criteria
  - Non-black/non-white race participants.
  - Participants with prior history of heart failure at baseline
  - End-stage renal disease at baseline

Exposures
  - Anemia, which will be primarily defined as hemoglobin concentrations of below 13.0 g/dL in men and 12.0 g/dL in women, according to the WHO recommendations.[20] We will repeat the analysis using other thresholds proposed by Beutler et al., based on Scripps-Kaiser and NHANES-III data for the 5th percentiles (Supplementary Table 1).[21]

  - CKD measures (given the availability of albuminuria and subsequent outcomes, visit 4 will be used for primary analysis but prior visits will be used for sensitivity analysis of eGFR)
    - eGFR: calculated from CKD-EPI equations based on serum creatinine and/or cystatin C
      - eGFR will be modeled as continuous variable with its splines and also will be stratified to the following categories: 90+, 60-89, 30-59, 0-29 ml/min/1.73m^2 [22]
    - Urine ACR (will be treated as continuous and categorical [0-9, 10-29, 30-299, and 300+ mg/g] variables)[22]

Outcome
  - Incident heart failure, which will be primarily defined as hospitalization or death with *International Classification of Diseases, Ninth Revision (ICD-9)* discharge codes of 428.x, or *Tenth Revision (ICD-10)* discharge codes of I50.x. We will secondarily analyze HF based on physicians' adjudication from 2005 onward.

Other variables of interest and covariates:
  Demographics
    - Age
    - Gender
    - Race
  Physical examination
    - Body mass index (BMI)
    - Systolic and diastolic blood pressure
  Life style and social economic status
    - Smoking status

- Alcohol consumption
  - Years of education
Medical history
  - Hypertension
  - Diabetes
  - Cardiovascular disease (at baseline and as a time-varying covariate)
  - Left ventricular hypertrophy (LVH) determined by electrocardiogram (ECG)
  - Atrial fibrillation (A-fib) determined by ECG and clinical history
  - Incident end-stage renal disease during follow-up (from USRDS linkage) as a time-varying covariate
Medication use
  - Aspirin
  - Angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB)
  - Beta blockers
  - Statin
Laboratory values
  - Low-density lipoprotein (LDL) cholesterol
  - High-density lipoprotein (HDL) cholesterol
  - Triglyceride (TG)
  - Cardiac damage markers (hs-cTnT)
  - hsCRP

Statistical Analysis Plan:
  - Baseline characteristics will be reported stratifying according to the presence or absence of anemia, and compared between with and without incident heart failure as well as across eGFR and ACR categories.
  - Between-group difference for continuous variables will be compared using t-tests for two-group, or one-way analyses for variance (ANOVA) for more than two groups. Categorical variables will be compared using chi-square tests.
  - Prevalence of anemia and its ratio at baseline will be assessed across cross-tabulated categories of eGFR and ACR proposed in the KDIGO CKD guidelines[19] using binomial regression. - A category of eGFR 90+ ml/min/1.73m^2 plus ACR 0-9 mg/g will be used as a reference group. Kaplan Meier curves will be used for assessing cumulative incidence rate of heart failure. Log-rank test will be used for comparing differences between groups.

  - Incidence rate of HF according to eGFR and ACR will be estimated using Poisson models. An Interaction term will be introduced into the models to assess an effect modification of anemia with CKD measures. If the interaction of anemia is identified, we will develop the models stratified by the presence or absence of anemia. Poisson models will be extended to estimate continuous change in incident rate across eGFR and ACR by relating to linear spline models with knots at 30, 60, and 90 ml/min/1.73m^2 for eGFR, and 10, 30, and 300 mg/g for log-transformed ACR.

- Hazard ratio of incident heart failure will be estimated using Cox proportional hazard models. If the interaction of anemia with CKD measures is found to be significant, the model will be stratified according to the presence of anemia.
- Models will be adjusted for covariates listed above.
- Several sensitivity analyses will be performed. First, we will repeat the stratified analyses in several clinical subgroups to assess effect modification. Second, we will repeat the analyses excluding prevalent cases at baseline and incident cases during follow-up of coronary heart disease in order to account for potential heart ischemia. Third, we will further adjust the model for incident end-stage renal disease in order to take account for potential impact of dialysis or transplantation, as these conditions have unique clinical procedures which may influence both anemia and HF risk.
- A two-sided p-value of less than 0.05 will be considered statistically significant. All statistical analyses will be conducted using STATA version 13 (StataCorp, College Station, TX)

Limitations
- Hemoglobin levels are available for selected participants at visit 4, and therefore statistical power may be limited for the analyses of ACR. Due to the nature of observational study, residual confounders may remain even after adjustment for various covariates.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ 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? __ X __ 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)?

Four studies potentially related to the current proposal have been proposed.
  - MP #863 in 2002, "The risk of left ventricular hypertrophy associated with moderate kidney dysfunction and anemia among African Americans"
  - MP #952 in 2003 "Anemia and kidney dysfunction as predictors of cardiovascular disease"
  - MP# 954 in 2003 "Electrocardiographic left ventricular growth associated with anemia and moderate kidney dysfunction"
  - MP #2086 in 2013, "Anemia and Heart Failure Incidence: the Atherosclerosis Risk in Communities Study"

Our primary outcome of interest will be incident heart failure, which is not an outcome of interest in #863, and #954. Primary outcome in #952 was cardiovascular disease, but the study looked at coronary heart disease and did not include heart failure as the outcome of interest.[23] MP #2086 aimed to look at the association of anemia with heart failure, as well as the effect modification by reduced kidney function. In this MP, however, kidney function was assessed base on visit 1 serum creatinine whereas we will primarily focus on eGFR based on serum creatinine and cystatin C as well as albuminuria, the other key element of CKD at visit 4. Also key authors of #2086, Kunihiro Matsushita and Josef Coresh are included in the present proposal.

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
        _X_   A. primarily the result of an ancillary study (list number* 2002.02)
        __   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.

[References]
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Supplementary Table 1: Second definition of anemia based on Scripps-Kaiser and NHANES-III data for the 5th percentiles

Group	Hemoglobin, g/dL
White men, y	
20-59	13.7
60+	13.2
White women, y	
20-49	12.2
50+	12.2
Black men, y	
20-59	12.9
60+	12.2
Black women, y	
20-49	11.5
50+	11.5

[a] Adopted and modified from Beutler et al.