ARIC Manuscript Proposal #2086

PC Reviewed: 2/12/13  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1. a. Full Title: Anemia and Heart Failure Incidence: the Atherosclerosis Risk in Communities Study  
   b. Abbreviated Title (Length 26 characters): Anemia and incident HF

2. Writing Group:  
Writing group members: Nowreen Haq, Sunil K. Agarwal, Abednego Chibungu, Laura Loehr,  
Patricia Chang (response awaited), Kunihiro Matsushita, Sumanta Mukherjee, Christine Sailer,  
Wayne Rosamond, Stuart Russell, Josef Coresh – others welcome.

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

First author: Nowreen Haq  
Address: 4100 North Charles Street, Apt #810, Baltimore, MD-21218  
Phone: 845-321-3084  Fax:  
E-mail: nhaq1@jhmi.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: Josef Coresh, MD, PhD  
Address: Welch Center for Prevention, Epidemiology & Clinical Research  
2024 E. Monument St., Suite 2-600  
Baltimore, MD 21287  
Phone: (410) 245-0495 Fax: (410) 955-0476  
E-mail: coresh@jhu.edu

3. Timeline: Data analysis to start after approval to start after approval of this manuscript proposal, first draft available by June, 2013
4. Rationale:

Anemia, as defined by the World Health Organization to be hemoglobin (Hgb) < 13.0 g/dl in men and <12.0 g/dl in women, is prevalent among heart failure (HF) patients. In large hospital registries of HF, a high prevalence of anemia (14-70%) has been reported, than general US population (5%) has been reported. It has consistently been shown that anemia is associated with higher morbidity and mortality in patients with HF. There is increased myocardial workload in chronic anemia, mediated through hemodynamic and neurohormonal changes, in order to achieve the cardiac output necessary to maintain tissue oxygenation. It is plausible that this adverse cardiac remodeling and contribute to the development of HF as has been shown in animal models. The mechanisms that cause anemia in HF, however, have not been fully elucidated. Another potential mechanism is mild renal dysfunction caused by the lower renal blood flow in HF may act as a mediator. It is believed mild dysfunction is not sufficient to impair erythropoietin (EPO) production, however, blunted EPO responses, in which EPO does not increase in proportion to the degree of anemia, have been shown. Chronic systemic inflammation may act as a common soil too. It is known that neurohormonal activation of proinflammatory cytokines can contribute both to both anemia of chronic disease as well as heart failure.

In above context whether anemia is associated with incidence of HF has not been studied. Also, whether there is heterogeneity in above association by age, race, gender, degree of renal dysfunction, and CHD remains unknown. Lastly, we will examine whether the above association is independent of incident CHD status.

5. Aims of this Proposal:

We hypothesize that patients with anemia in the ARIC study will have higher risk of developing HF independent of confounding variables.

Specific Aim #1: Estimate the association of baseline anemia with the incidence of heart failure and examine effect modification/confounding by kidney dysfunction, and CAD.

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 methodological limitations or challenges if present).

Study sample:
ARIC participants at visit 1 (excluding non-white and non-black; exclude those with prevalent HF defined by Gothenburg criteria; exclude those with missing important covariates).

Study design:
Time to event analysis using visit 1 as baseline and incident HF hospitalizations/death as outcome.

Data analysis:
**Exposure:** Anemia defined as Hgb < 12 g/dL in women and <13.0 g/dL in men

**Potential confounders:** We will consider baseline (1987-89) age, sex, race, hypertension, eGFR, HDL and LDL cholesterol, CHD, smoking status, pack years of smoking, alcohol intake (grams/week), diabetes and body mass index, available markers of inflammatory

**Analysis:** First, we will compare the mean and prevalence of the covariates by baseline anemia Status using standard definition. Using a Cox Proportional Hazards model, we will estimate the hazard ratio (HR) of HF by anemia status. Further, we will look at dose response relationship over Hgb level and hazards of anemia using linear/restricted cubic splines. We will examine heterogeneity of association by race, gender, age groups, CHD status, and CKD stages.

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
   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)? There are no proposals to study anemia and incidental heart failure.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ No
   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)* albuminuria, AS#_2002.02_)
      *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: