ARIC Manuscript Proposal #2481

PC Reviewed: 12/9/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Iron status and incidence of cardiovascular events. The ARIC study.

1.b. Abbreviated Title: Iron status and cardiovascular events

2. Writing Group:
Writing group members: Odilson Marcos Silvestre, Alexandra Gonçalves, Brian Claggett, Wilson Nadruz Junior, XXXXXX, XXXXXX, XXXXXX, ……, XXXXXXXX, Scott D. Solomon, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **_OMS_ [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: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months.

4. Rationale:

Alterations in iron metabolism, either deficiency or overload, have been associated with damage to the cardiovascular system.[1] Increases in body iron store are associated with oxidation of low density lipoprotein cholesterol[2], oxidative stress, endothelial dysfunction and acceleration of atherosclerosis.[3] Likewise, iron deficiency has been related to oxidative stress[4] and inflammation,[5] although the relationship with cardiovascular disease remains controversial.

It is acknowledged that severe iron overload secondary to hemochromatosis may lead to heart failure,[6] regardless of the presence of coronary disease. High iron levels lead to iron deposit into cardiomyocytes provoking direct cell damage and consequent left ventricular remodeling and dysfunction.[7] Additionally, some authors suggest that iron overload can increase the risk of coronary heart disease even in the absence of hemochromatosis.[1] This relationship is supported by the known association between iron storage and cardiovascular risk factors, especially type 2 diabetes[8] and metabolic syndrome.[9,10] Nevertheless, the majority of epidemiological studies have failed to confirm a relationship between iron overload and coronary disease or stroke.[11,12] Therefore, there are conflicting findings and scarce data in the role of non-hemochromatosis iron overload in the incidence of heart failure.

Similarly, studies about the impact of iron deficiency in cardiovascular disease have provided contradictories results.[13,14] Iron deficiency is associated with an ominous prognosis in patients with heart failure[15] and a study on elderly population showed that iron deficiency was independently associated with cardiovascular mortality.[13] However, some authors have speculated that iron deficiency can protect against cardiovascular disease.[16]

In the United States, the prevalence of iron deficiency is estimated of 11% in women and 1% in men[18] and iron overload related to hemochromatosis of 0.5-1%. In consequence, the identification of an association between iron imbalance and cardiovascular disease can have a great impact in health care.

This study aims to evaluate the association between iron status and incidence of cardiovascular events (stroke, coronary disease, and heart failure) and death in the population of the ARIC study.

5. Main Hypothesis/Study Questions:

Iron imbalance, presented either as iron overload or iron deficiency, is associated with a higher rate of cardiovascular events (heart failure, stroke, coronary disease) and death.

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 Design and Inclusion/Exclusion Criteria:

We will perform an analysis of iron status based on ferritin serum levels from Visit 1 and evaluate the association with stroke, heart failure, coronary disease and death through the period until visit 5. The study sample will include all patients who had measured the ferritin level in Visit 1 (1987-1989). We will exclude patients with stroke, coronary disease and heart failure diagnosed at Visit 1.

Variables to be evaluated

Exposures variables:
1) Ferritin levels evaluated as continuous variable and categorized on ferritin levels:[19]
   a. Iron defeciency (ferritin≤15 mcg/L)
   b. Normal range (ferritin between 15-200 mcg/L)
   c. Iron overload (ferritin≥200 mcg/L)

Outcome variables:
Incidence of heart failure, stroke, coronary artery disease (myocardial infarction or angina) and death.

Potential covariates:
Demographic characteristics (age, race, sex, body mass index, ARIC center), cardiovascular risk factors (arterial hypertension, dislipidemia, alcohol consumption, smoking status, LDL-C, HDL-C), blood pressure, use of antihypertensive medications or statins, glucose, plasma lipid levels (i.e. HDL and LDL cholesterol, triglycerides), inflammatory markers (C-reactive protein and interleukin-6), creatinine clearance, hemoglobin.

Analytical approach:
Continuous normally distributed data will be displayed as mean and standard deviation and continuous non-normally distributed data will be displayed as median and interquartile range. Categorical data will be reported as percent frequencies and compared by chi-squared or Fischer exact tests. Continuous data will be compared by Wilcoxon rank sum test, t test, Kruskall-Wallis test and 1-way ANOVA followed by Bonferroni test as appropriate. Associations between ferritin and cardiovascular events will be evaluated using multivariable logistic regression analyses adjusting for the significant covariates. Analysis on the effect of ferritin in the incidence of heart failure, stroke, coronary artery disease (myocardial infarction or angina) and death will be performed using Cox proportional hazards model. We will create a univariate and a multivariate model to identify both the unadjusted and adjusted risk of the outcome of interest. The multivariate model will include the potential confounders: age, race, sex, body mass index, ARIC center, arterial hypertension, dislipidemia, alcohol consumption, smoking status, C-reactive protein, interleukin-6, creatinine clearance, and hemoglobin. P-values <0.05 will be considered significant.

Limitations:

A limitation of this study is that ferritin is the only marker of iron status and its serum level can be influenced by inflammation. To minimize this limitation, inflammatory markers, such as C-reactive protein and interleukin-6, will be included as covariates in the model for analysis. Additionally, the sample is composed by patients without diabetes in visit 1, which limits the results for non-diabetes patients.

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.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)?

1- Hemochromatosis gene polymorphism and incident CHD. Manuscript #599

Rasmussen ML, Folsom AR, Catellier DJ, Tsai MY, Garg U, Eckfeldt JH. A prospective study of coronary heart disease and the hemochromatosis gene (HFE) C282Y mutation: the Atherosclerosis Risk in Communities (ARIC) study. Atherosclerosis. 2001 Feb 15;154(3):739-46.

2- Association of plasma ferritin and incident diabetes. Manuscript # 946

A prospective study of plasma ferritin level and incident diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Jehn ML, Guallar E, Clark JM, Couper D, Duncan BB, Ballantyne CM, Hoogeveen RC, Harris ZL, Pankow JS. Am J Epidemiol. 2007 May 1;165(9):1047-54.

3- Moore M, Folsom AR, Barnes RW, Eckfeldt JH. No association between serum ferritin and asymptomatic carotid atherosclerosis. The Atherosclerosis Risk in Communities (ARIC) Study. Am J Epidemiol. 1995 Apr 15;141(8):719-23.

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)* #946)

*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.

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