ARIC Manuscript Proposal #2375

PC Reviewed: 6/10/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Sickle cell trait and coronary heart disease

b. Abbreviated Title (Length 26 characters): **sickle cell trait and CHD and CHF**

2. Writing Group:

Writing group members: Aaron Folsom, Alex Reiner, Jim Wilson, Hyacinth Hyacinth, Rakhi Naik, Nigel Key, Vimal Derebail, Abhi Kshirsagar, Suma Konety, Morgan Grams, Robert Adams, Nora Franceschini

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

F**irst author**: **Alex Reiner**
Address: University of Washington
Box 357236
Seattle WA 98195
Phone: (206) 667-2710
E-mail: apreiner@uw.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: **Aaron Folsom**
Address: 1300 S 2nd St #300, Minneapolis, MN 55415
Phone: (612) 626-8862
E-mail: folso001@umn.edu

3. Timeline: Manuscripts to be completed in 6 months, following incorporation of genotyping of sickle cell trait polymorphism (rs334) into data set and data analysis.

4. Rationale:

Sickle cell disease is a recessive condition due to homozygosity for a mutation in the beta-globin gene, resulting in the formation of hemoglobin S (HbS) which polymerizes under conditions of dehydration and/or acidosis and gives sickle cells their characteristic shape [1]. The homozygous or HbSS genotype is associated with a global activation and increased plasma levels of prothrombotic mediators/factors and with a 300 fold increase in stroke risk among children with SCD compared with non-SCD [2]. The heterozygous

form of sickle cell disease referred to as sickle cell trait (SCT) or HbAS has one normal β-globin gene and one sickle Hb gene. Laboratory assays of SCT carriers indicate increased blood viscosity, abnormal erythrocyte adhesion to the vascular endothelium, and decreased red cell rigidity, all of which contribute to microvascular occlusion and are amplified in the setting of hypoxia and exertion [3-5].

While it is generally accepted that individuals with sickle cell trait do not have a reduced life expectancy, many complications, including splenic infarction, renal papillary necrosis, hyposthenuria, renal medullary carcinoma, rhabdomyolysis, gross hematuria, and sudden death have been described [1]. These events likely reflect exacerbations of low-level rates of sickling in response to changes in intravascular oxygen tension, pH, volume status, osmolality, and temperature. Associations with other potential end-organ vaso-occlusive pathologies, such as CVD and CHF are less clear [6,7]. While multiple case reports have described acute myocardial infarction in patients with sickle cell disease and minimal coronary artery disease (CAD), other epidemiological studies have suggested that sickle cell disease might actually be protective from atherosclerotic disease of the coronary vessels [8-12]. Congestive heart failure (CHF) is a known common complication of sickle cell disease, most often as a consequence of chronic anemia [13,14]

The purpose of this study was to quantify the risk of cardiac complications associated with sickle cell trait. We propose to examine the association of SCT with the incidence of CHD and CHF, in African American participants of the ARIC cohort. MI, coronary revascularization, fatal CHD, and CHF have been identified in the ARIC study by annual, standardized questionnaires with a diagnostic algorithm[40], and hospital surveillance[41]. SCT trait genotyping has been funded by an ancillary study, and is ongoing at the central research laboratory. Genotyping is complete, and we have been given express permission by the ancillary study to use this variable.

5. Main Hypothesis/Study Questions:

Is sickle cell trait associated with risk of incident CHD (including, MI, fatal CHD, and coronary revascularization?
Is sickle cell trait associated with risk of incident CHF?

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).

Sickle cell trait will be defined by heterozygosity for hemoglobin S (single nucleotide polymorphism rs334). Our study will be restricted to participants with either heterozygous SCT or normal hemoglobin; thus, participants with known or detected homozygosity for hemoglobin S, hemoglobin C, or concomitant presence of hemoglobin

S and C will be excluded. Hemoglobin S and C is being genotyped in ancillary study 2010.16.

To examine associations between SCT and the prevalence and incidence of CHD, we will include all African Americans in the ARIC cohort with blood sample available for genotyping. For the purposes of this analysis, CHD will include non-fatal MI, CHD death, and coronary revascularization. Hazard ratios for incident CHD events will be analyzed by Cox regression. Associations between sickle cell trait and CHD will be adjusted to control for the traditional risk factors for cardiovascular disease (age, gender, blood pressure and antihypertensive meds, smoking, diabetes, hypercholesterolemia)[1].

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 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?
__x__ Yes ____ 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"?
__x__ 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)?

Ancillary study # 2010.16 Sickle cell trait: a risk factor for kidney disease?
We have contacted the lead authors and are collaborating with them on this 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* 2010.16**)**

___ 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.

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