

## ARIC Manuscript Proposal #2349

PC Reviewed: 4/8/14

Status: A

Priority: 2

SC Reviewed: \_\_\_\_\_

Status: \_\_\_\_\_

Priority: \_\_\_\_\_

**1a. Full Title:** The relationship between sickle cell trait and abnormalities of cardiovascular structure and function

**b. Abbreviated Title (Length 26 characters):** Sickle cell trait & echo

**2. Writing Group:** Natalie A. Bello, Susan Cheng, Amil M. Shah, Brian Claggett, Vimal Kumar Derebail, Abhijit Kshirsagar, Nigel S. Key, Aaron Folsom, Scott D. Solomon, Suma H. Konety, OTHERS WELCOME.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. NAB [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 immediately following proposal approval and the acquisition of genotype data with the aim of completing analyses and a manuscript within 3 months of proposal approval.

### **4. Rationale:**

Sickle cell trait (SCT), defined as heterozygosity for the sickle cell beta-globin gene (HbAS), has traditionally been considered a benign carrier state that has persisted due to the protective effect it imparts against severe falciparum malaria. Approximately 8-10% of African Americans are carriers of this trait.<sup>1,2</sup> Despite a lack of high-quality longitudinal studies of individuals with

sickle cell trait, it is generally thought that carriers exhibit a normal lifespan. Several studies of patients with sickle cell anemia (HbSS) have shown an association with abnormalities of cardiac structure and function including increased atrial volumes, LV mass, pulmonary hypertension, and bi-ventricular dilation<sup>3,4,5</sup> Despite the reasonably high prevalence of the HbAS trait amongst African Americans there is a paucity of data on whether sickle cell trait is associated with abnormalities of cardiac structure and function, or with incident heart failure.

We propose to examine the association of SCT with cardiac structural and functional changes, in African American participants of the ARIC cohort. SCT trait genotyping has been funded by an ancillary study, and we have been given permission by the ancillary study to use this variable.

### **5. Main Hypothesis/Study Questions:**

We hypothesize that African American participants who are carriers of SCT will have more abnormalities of cardiac structure including increased left ventricular mass and remodeling and abnormal diastolic function, as well as abnormal right ventricular function and higher estimated pulmonary arterial pressure than non-carriers (HbAA). We further hypothesize that sex may modify these relationships.

Thus, our specific study aim is:

1. To examine the cross-sectional association between the presence of HbAS and variations in cardiac structure and function.

### **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).**

**Study Design and Inclusion/Exclusion Criteria:** Our study will include African American participants heterozygous for SCT (HbAS) or with normal beta-globin (HbAA) who underwent echocardiography during Visit 5 (2011-2013) and have consented to the use of genetic material. Participants with known or detected homozygosity for hemoglobin S, hemoglobin C, or compound heterozygotes for hemoglobin S and C will be excluded.

**Exposure variable:** The presence of HbAS defined as heterozygosity for the hemoglobin S allele (rs334).

### **Outcome variables:**

The primary analysis will be to evaluate the association of SCT on the following parameters of cardiac structure and function:

1. Left ventricular (LV) dimensions, volumes, and ejection fraction
2. Global LV systolic strain (longitudinal, circumferential, radial)
3. LV diastolic function
4. Left atrial volume
5. Right ventricular dimensions, volumes, ejection fraction
6. Estimated pulmonary artery systolic pressure.

### **Statistical Analysis:**

Descriptive statistics of the study sample will be presented by the presence of HbAS compared to HbAA. Continuous normally distributed data will be displayed as mean and standard deviation values; continuous non-normally distributed data will be displayed as median and interquartile range values. Categorical data will be reported as counts and percent frequencies. Categorical variables will be compared via  $\chi^2$  or Fisher's exact test, while continuous data will be compared between groups via t-test or Wilcoxon rank sum as appropriate.

Univariate and multivariable linear or logistic regression analysis will be used to examine the cross-sectional association of HbAS and echocardiographic characteristics at visit 5. Adjustments for age, field center, height, weight, and clinical characteristics (traditional CV risk factors like diabetes, hypertension, dyslipidemia, smoking status), alcohol use, COPD, asthma will be performed. We will test for multiplicative effect modification of sickle cell trait by sex using cross-product terms. A two-sided p-value of <0.05 will be considered statistically significant.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**

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?**

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  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>**

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 other proposals submitted to examine the relationship between sickle cell trait and cardiovascular structure and function.

There are five proposals related to sickle cell trait:

2150 Sickle cell trait and venous thromboembolism

2174 Is sickle cell trait a risk factor for stroke and cerebral small vessel disease?

2025 Sickle cell trait as a contributing factor to increased cardiovascular and stroke risk disparity in African Americans.

2263 Is sickle cell trait a risk factor for kidney disease?

Unnumbered proposal for a multi-study meta analysis of sickle cell trait and incident CHD/HF outcomes by Alex Reiner

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?**

Yes     No

**11.b. If yes, is the proposal**

**A. primarily the result of an ancillary study (list number(s)\* 2009.12, 2010.16, 2012.10)**

**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.csc.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.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

## References:

<sup>1</sup> Motulsky AG. Frequency of sickling disorders in U.S. blacks. N Engl J Med. 1973;288:31-3.

<sup>2</sup> Michlitsch J, Azimi M, Hoppe C, et al. Newborn screening for hemoglobinopathies in California. Pediatr Blood Cancer. 2009;52:486-90.

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<sup>3</sup> Knight-Perry JE, de Las Fuentes L, Waggoner AD, et al Abnormalities in cardiac structure and function in adults with sickle cell disease are not associated with pulmonary hypertension. *J Am Soc Echocardiogr.* 2011;24:1285-90.

<sup>4</sup> Poludasu S, Ramkissoon K, Saliccioli L, Kamran H, Lazar JM. Left ventricular systolic function in sickle-cell anemia: a meta-analysis. *J Card Fail.* 2013;19:333-41.

<sup>5</sup> Estrade G, Poitrineau O, Bernasconi F, Gernier D, Donatien Y. Left ventricle function and sickle-cell anemia. *Arch Mal Coeur Vaiss.* 1989;82:1975-81.