ARIC Manuscript Proposal # 1669

PC Reviewed: 7/13/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Incidence and risk factors of sick sinus syndrome in a population-based cohort: the ARIC study**

b. Abbreviated Title (Length 26 characters): **SSS in ARIC**

2. Writing Group: Alvaro Alonso, Lin Y. Chen, Richard S. Crow, Cameron Guild, Aaron R. Folsom, others welcome

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

First author: Alvaro Alonso
Address: 1300 S 2nd St, Suite 300
University of Minnesota
Minneapolis, MN 55454
Phone: 612 626 8597 Fax: 612 624 0315
E-mail: alonso@umn.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 R. Folsom
Address: Div of Epidemiology & Community Health
University of Minnesota
1300 S 2nd St, suite 300. Minneapolis, MN 55454
Phone: 612-626-8862 Fax: 612-624-0315
E-mail: folso001@umn.edu

3. Timeline:
Data analysis – 3 months
First draft of the manuscript – 3 months

4. Rationale:
Sick sinus syndrome (SSS) is a disorder characterized by symptomatic sinus node dysfunction. In the electrocardiogram (ECG), SSS is usually manifested as sinus bradycardia, sinus arrest, or sinoatrial block, sometimes accompanied by supraventricular tachyarrhythmias ("tachy-brady" syndrome). Most individuals with sinus node dysfunction are asymptomatic. Typical symptoms of SSS include syncope, dizziness, palpitations, heart failure, or angina.[1]

SSS affects mostly elderly individuals, without a clear gender predilection.[2] The etiology of SSS is unknown in most cases, usually linked to degenerative fibrosis of the sinus node tissue. Other possible etiologies include use of some cardiovascular medications (digitalis, beta-blockers, calcium channel blockers, antiarrhythmics), cardiac disorders (cardiomyopathies, myocarditis, pericarditis, ischemia), and other less frequent disorders, such as rheumatic disorders or neoplasias. Pacemaker implantation is the best therapy for patients with SSS.

Though SSS accounts for up to 50% of indications for pacemaker indications in the US,[3] little research has been done on the epidemiology of this disorder. No information exists on the incidence and risk factors for SSS in the general population. Similarly, there is not reliable information to determine the impact of SSS on overall mortality and the future risk of cardiovascular disease. We propose to study the epidemiology of SSS in the ARIC cohort, taking advantage of its long follow-up and the availability of hospital discharge codes.

5. Main Hypothesis/Study Questions:

1. To calculate the age, gender, and race-specific incidence of hospitalized SSS in the ARIC cohort
    a. Based on the ARIC rates, we will estimate the annual number of new cases of hospitalized SSS in the general US population aged 45-84.
2. To determine the principal risk factors for hospitalized SSS in the ARIC cohort
3. To evaluate the association of hospitalized SSS with mortality and CV outcomes.

We hypothesize that SSS will be more frequent in men than women, and in older than younger individuals. If SSS shares pathogenic mechanisms with atrial fibrillation, we will see a lower incidence in African-Americans compared to whites. We expect to find a higher risk of SSS in ARIC participants with a worse cardiovascular risk profile. Lastly, we hypothesize that individuals with SSS will have a higher risk of total and CV mortality compared to those without it, even after adjustment for CV risk factors.

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

We will conduct a follow-up analysis of ARIC cohort participants, using visit 1 as baseline. We will exclude individuals of race other than white or black, those with atrial fibrillation or a pacemaker at baseline, and those with heart rate below 50 beats per minute not on beta-blockers.

Outcome ascertainment

SSS will be identified from hospital discharge codes (ICD9 code: 427.81). We will exclude SSS events identified in the first 3 years of follow-up (to avoid including prevalent cases). A second, more restricted definition of SSS, will require presence of ICD9 code 427.81 as a primary discharge diagnosis or 427.81 code in any position plus a code for pacemaker implantation during the follow-up. ICD9 codes for pacemaker implantation are:

- 37.8 Insertion, replacement, removal, and revision of PM device: 37.80, 37.81, 37.82, 37.83, 37.85, 37.86, 37.87, 37.89

- V45.01: Status post-implantation of cardiac pacemaker
- V53.31: Fitting and adjustment of cardiac pacemaker

In a review of 29 hospital discharge summaries and available ARIC hospital charts in the Minnesota field center with an ICD9 code of 427.81, 17 of them confirmed the diagnosis of SSS, in 3 cases there was not enough information to classify individuals as having SSS, in 1 case there was a coding error, and another case had digitalis toxicity, which was coded as SSS (83% positive predictive value). Using the more specific SSS definition (427.81 as primary discharge code or 427.81+pacemaker), 22 out of 24 cases were confirmed (92% positive predictive value). These numbers suggest an adequate specificity of the ICD9 code.

Assessment of covariates

Covariates of interest for the present analysis, all measured at baseline, include:

- Age, gender, race, field center, education
- Systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, total cholesterol, HDL-cholesterol, body mass index, smoking (current, former, never), sports-related physical activity, alcohol intake (grams/week)
- Prevalence of CHD, heart failure or stroke

Statistical analysis

Person time of follow-up for each ARIC participant will be calculated from baseline to the date of SSS incidence, death or December 31, 2007, whichever comes earlier. We will compute age, sex, and race-specific incidence rates. These incidence rates will be applied to the general US population (US census 2000) to estimate the number of SSS cases in the US each year.
The association of lifestyles, CV risk factors and prevalent CVD with the incidence of SSS will be estimated using Cox models, with time to SSS incidence as the main outcome variable.
Finally, the association of SSS with mortality and CVD will be estimated in Cox models with a time-varying indicator for the incidence of SSS, adjusting for CV risk factors at baseline, and incidence of HF, CHD and stroke as time-dependent covariates during the follow-up.

Strengths and limitations

The strengths of this study include the ethnic diversity of ARIC, the long follow-up, and the availability of information on cardiovascular risk factors and CVD incidence.
Major limitations of the study are the method of SSS ascertainment, which has limited validity and probably suboptimal sensitivity, and the expected reduced number of SSS cases (<200). Nonetheless, this will be the first population-based study of SSS incidence.

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)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes _X_ No

11.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)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.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

1. Adán V, Crown LA. Diagnosis and treatment of sick sinus syndrome. *Am Fam Physician.* 2003;67:1725-1732.

2. Lamas GA, Lee K, Sweeney M, Leon A, Yee R, Ellenbogen K, Greer S, Wilber D, Silverman R, Marinchak R, Bernstein R, Mittleman RS, Lieberman EH, sullivan C, Zorn L, Flaker G, Schron E, Orav EJ, Goldman L. The Mode Selection Trial (MOST) in sinus node dysfunction: design, rationale, and baseline characteristics of the first 1000 patients. *Am Heart J.* 2000;140:541-551.

3. Bernstein AD, Parsonnet V. Survey of cardiac pacing and defibrillation in the United States in 1993. *Am J Cardiol.* 1996;78:187-196.