ARIC Manuscript Proposal # 3368

PC Reviewed: 3/12/18 **Status: _____** **Priority: ____**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Life's Simple 7 Cardiovascular Health Score and Premature Atrial Contractions: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Life's Simple 7 score and PACs

2. Writing Group:

Writing group members: Darshan Krishnappa, Wendy Wang, Mary R. Rooney, Faye L. Norby, Niki Oldenburg, Elsayed Z. Soliman, Alvaro Alonso, Jin O-Uchi, Samuel C. Dudley, Jr., Pamela L. Lutsey, Lin Yee Chen

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **DK**

First author: **Darshan Krishnappa, MD**
Address: Cardiovascular Division
Department of Medicine
University of Minnesota Medical School
420 Delaware St SE, MMC 508
Minneapolis, MN, 55455

Phone: 6122297747
E-mail: darshankrishnappa@gmail.com

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: **Lin Y Chen MD MS**
Address: Cardiovascular Division
Department of Medicine
University of Minnesota Medical School
420 Delaware St SE, MMC 508
Minneapolis, MN, 55455

Phone: (612) 625-4401 Fax: (612) 626-4411
E-mail: chenx484@umn.edu

3. Timeline:
We will complete analysis within 1month of manuscript proposal approval
We will complete the first draft within 3 months of manuscript proposal approval

4. Rationale: Premature atrial contractions (PACs) are frequently encountered and for long have been considered a benign entity. However, more recently this assumption has been questioned because an increasing number of studies have shown an association between PACs and risk of atrial fibrillation (AF). (1–5) Further, PACs have also been found to be associated with an increased risk of stroke independent of AF, (6) though this has been postulated to be related to the occurrence of subclinical AF. The association between PACs and AF has led to increased efforts towards suppression of PACs, with elimination of PAC triggers of AF forming the basis of catheter ablation for paroxysmal AF.

Risk factors for AF include advancing age, hypertension, diabetes mellitus, valvular heart disease, heart failure and coronary artery disease. (7) These factors are thought to be associated with LA structural remodeling, thereby explaining their association with an increased risk for AF. However, their impact on PACs—which are the triggers initiating AF—is poorly understood. More recently, Conen et al. in a study analyzing 24 hour Holter recordings found an association between increasing age, history of cardiovascular disease, lower high density lipoprotein cholesterol levels and lower physical activity and PAC frequency; this study, however, was limited by the quantification of PACs based on a single 24 hour Holter recording.

Life's Simple 7 (LS7) cardiovascular score was developed by the American Heart Association and has been shown to be a powerful predictor of cardiovascular outcomes with lower scores associated with higher risk of cardiovascular disease, heart failure, AF, and stroke. (8–12) In this study we aim to identify risk factors for PACs in a community dwelling study population and assess the association between Life's Simple 7 score and PAC frequency.

5. Main Hypothesis/Study Questions:
(1) To evaluate the association of Life's Simple 7 (LS7) score at visit 3 with PAC burden at visit 6. We hypothesize that compared to participants with low LS7 scores, those with optimal LS7 scores at visit 3 will have lower PAC burden at visit 6.

(2) To identify which LS7 factors at visit 3 are associated with higher PAC burden at visit 6. We hypothesize that higher BMI and lower physical activity at visit 3 will be associated with higher PAC burden at visit 6.

(3) To determine the cross-sectional (visit 6) association of LS7 risk factors obtained in late-life with PAC burden. * We hypothesize that those with optimal LS7 scores at visit 6 will have lower PAC burden at visit 6 compared with those with low LS7 scores at visit 6.

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

Ho 1&2: Prospective cohort from visit 3 to visit 6 (when the Zio XT Patch device was applied).
Ho 3: Cross-sectional at visit 6.

Inclusion/Exclusion:

Participants who wore the Zio XT Patch and had complete data on the LS7 characteristics will be included in this analysis. Patients with a diagnosis of permanent atrial fibrillation will be excluded from the study. Patients with PACs on visit 3 ECG will be excluded from analysis.

Variables

Exposure: LS7 risk factors will be classified as has been done previously in ARIC (see table below).(13) LS7 will be represented in two different ways: each risk factor will be analyzed individually, and also as an overall composite score. A composite score ranging from 0-14 will be created, in which each risk factor is given points of 0, 1, or 2 for poor, intermediate, or ideal, respectively. The score will be categorized as inadequate (0-4), average (5-9), or optimum (10-14) cardiovascular health.(13)

Risk factor	**Ideal**	**Intermediate**	**Poor**
Physical activity	$\geq$ 150 min/week moderate or $\geq$ 75 min/week vigorous or $\geq$ 150 min/week moderate + vigorous	1-149 min/week moderate or 1-75 min/week vigorous or 1-149 min/week moderate + vigorous	None
Total cholesterol	<200 mg/dL, without medication	200-239 mg/dL or treated to <200 mg/dL	$\geq$240 mg/dL
Blood pressure	<120/<80 mmHg, without medication	SBP 120-139 or DBP 80-89 mmHg or treated to <120/<80 mmHg	SBP $\geq$ 140 or DBP $\geq$ 90 mmHg
Body mass index	< 25 kg/m^2	25-29.99 kg/m^2	$\geq$ 30 kg/m^2
Fasting blood glucose	< 100 mg/dL, without medication	100-125 mg/dL or treated to < 100 mg/dL	$\geq$ 126 mg/dL
Smoking status	Never or quit >12 mo	Former $\leq$ 12 mo	Current
Diet[†]	4-5 components	2-3 components	0-1 components

[†]Responses to the modified Willet food frequency questionnaire (FFQ) were used to construct the LS7 healthy diet score based on how many of the following five diet goals are met: > 4.5 cups of fruits and vegetables per day, > 2 servings of at least 3.5 ounces of fish per week, < 1500 mg of sodium per day, < 450 kcal of sugar-sweetened beverages per week, > 3 servings of 1-oz servings of whole grain (1.1 gram of fiber per 10 grams of carbohydrate).

Outcomes

PAC burden; PAC count will be calculated based on the number of isolated, couplet, and triplet PACs [e.g. # isolated PACs + 2 * (# couplet PACs) + 3 * (# triplet PACs)]. PAC burden will be defined as PAC count per day.

Other confounders/covariates

Age, sex, race, center, education, alcohol intake, diet, physical activity, smoking status, hypertension, diabetes mellitus, dyslipidemia, body mass index, heart failure, left ventricular ejection fraction, drugs including betablockers, calcium channel blockers, digoxin, amiodarone, CHD, HDL cholesterol, LDL cholesterol, stroke, atrial fibrillation.

Statistical analysis

- Participant characteristics will be described using mean ± SD for continuous variables and proportions for categorical variables, stratified by LS7 classifications.
- PAC burden will be compared across LS7 categories.
- Multinomial logistic regressions will be used to evaluate the relationship between the LS7 composite score with PAC burden, as well as for each LS7 risk factor with PAC burden individually.
    - Model 1 will be adjusted for age, sex, race/center
    - Model 2 will be adjusted for model 1 plus education, alcohol intake
    - Model 3 will be adjusted for model 2 plus prevalent CHD, HDL cholesterol, LDL cholesterol, prevalent stroke
- Inverse probability weighting will be used to account for attrition due to death or visit 6 non-attendance.
- Interactions by age (median split), race and sex will be evaluated by including cross-product terms in the models.

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? ____ 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/mantrack/maintain/search/dtSearch.html

___**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)?
#2966: LS7 & AF in ARIC (Garg)
#2280: Zio arrhythmia burden (Rooney)

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* 2013.14)
___ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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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