ARIC Manuscript Proposal # 3135

PC Reviewed: 3/20/2018 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1. a. Full Title:
Association of Anger, Depressive Symptoms, and Poor Social Support with the Risk of Incident Atrial Fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
Emotional distress and AF risk

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

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3. Timeline:
March 2018 – Submit proposal
April-May-June 2018 – Complete primary data analysis
June 2018 – Submit as abstract to AHA Scientific Sessions
July-August-September-October 2018 – Additional data analysis/Manuscript preparation
November-December 2018 – Submit manuscript for P&P review

4. Rationale:

Atrial fibrillation (AF) is the most commonly presenting cardiac arrhythmia in clinical practice, with an estimated prevalence of up to 12 million people in the United States by 2050.[1,2] AF is a major source of morbidity and rising health care costs.[3,4] Although prior research into AF risk factors has allowed for a better understanding of its causation and prediction, over 40% of the risk attributed to AF still remains unexplained after accounting for established risk factors.[5] Continued investigation into identifying additional risk factors is important to improve our understanding of the mechanisms that cause AF.

Emotional distress has been suggested as a potential risk factor AF through effects on the autonomic nervous system and hypothalamus-pituitary-adrenal axis.[6,7] The catecholamine stimulation that results from these emotional states may also affect the electrophysiological properties of the heart including altered conduction across the sinus and AV nodes and increased P-wave dispersion, both of which can increase susceptibility of AF.[8,9] Abnormalities in markers of sympathetic and parasympathetic tone have been reported in affective disorders such as depression and panic disorder.[10,11]

Previous literature examining the prospective relationship between emotional distress and incident AF is limited and results are mixed. Initial studies, performed in predominantly white populations, reported that depression and chronic stress were not associated with AF while anger, hostility, and tension were, but only in men.[12-15] More recently, we demonstrated in a multi-ethnic cohort that depressive symptoms were associated with incident AF; however, there were no associations observed for anger, anxiety, or chronic stress.[16] We seek to build upon current literature and examine the association of several psychosocial measures indicative of underlying emotional distress with incident AF in a well-characterized, biracial cohort.

5. Main Hypothesis/Study Questions:

1) To investigate associations of anger, depressive symptoms, and poor social support with risk of incident AF in a multi-ethnic cohort
2) To investigate whether associations of these measures with risk of incident AF differ when stratified by sex or race

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).

Data:

Study participants

Eligible participants will be from the ARIC cohort attending Visit 2 (1990-1992) with examination data on psychosocial measures—anger, depressive symptoms, and social support, and vital exhaustion. Visit 2 will serve as the baseline visit for this analysis.

Exposure Variables—Anger, Depressive Symptoms, and Social Support—From Visit 2

1) *Anger* was measured by the Spielberger Trait Anger scale, which includes 10 items assessing extent and frequency of experiencing anger.[17] Each item has a 4-point response from “almost never” (“1”) to “almost always (“4”) and scores are summed across items to create a Trait Anger score (range, 10 to 40). High trait anger will be defined by scores of 22 to 40, moderate anger by scores of 15 to 21, and low anger by

scores of 10 to 14.[18-20] Scores will be stratified in approximate quartiles or tertiles, based on the distribution of scores, to evaluate potential threshold effects.

2) *Depressive symptoms* were determined via a 21-item Vital Exhaustion Questionnaire.[21] Vital exhaustion is defined as excessive fatigue, feelings of demoralization, and increased irritability and is often considered a form of adaptation to prolonged distress.[21,22] The questions represented three categories: (1) vegetative depressive symptoms (fatigue, sleep pattern, energy and concentration); (2) nonvegetative symptoms (crying spells, hopelessness, irritability, decreased libido and suicidality); and (3) functional depressive symptoms (coping and productivity). Responses are summed to obtain an overall vital exhaustion score, which ranges from 0 to 42, with higher scores representing more depressive symptoms. The correlation of vital exhaustion and depression, measured by the Beck Depression Inventory, is 0.62.[23] As established cut-offs do not exist, scores will be stratified in approximate quartiles or tertiles, based on the distribution of scores, to evaluate potential threshold effects.
3) *Social Support* was assessed using the short form of the Interpersonal Support Evaluation List [ISEL-SF] and the Lubben Social Network Scale [LSNS].[24,25] Both questionnaires are psychometrically valid and routinely applied instruments to measure perceived social support.[26,27]
   - The 16-item ISEL-SF measures an individual's perception of his or her appraisal support, tangible assets, belonging support and self-esteem support. Each question of the ISEL-SF is scored on a 4-point rating scale (definitely true, probably true, probably false and definitely false; scored 0–3). The total (summed) score is an aggregate index of social support, with higher scores indicating greater levels of perceived interpersonal support.[27] As established cut-offs for ISEL-SF scores do not exist, scores will be stratified in approximate quartiles or tertiles, based on the distribution of scores, to evaluate potential threshold effects.
   - The LSNS is a self-assessed measure of the size and availability of one's active social network of family, friends and peers, consisting of 10 questions on a 0–5 rating scale. Total scores range from 0 to 50 and are classified based on established levels of risk for social isolation: socially 'isolated' (≤20), 'high risk' for isolation (21–25), 'moderate risk' for isolation (26–30) and 'low risk' for isolation (≥31). 3 groups will be created based on scores of ≤25, 26-30, and ≥31. The 'isolated' and 'high risk' are collapsed because few participants score within the 'isolated' range.[28]

<u>Outcome Variable—Atrial Fibrillation</u>

Incident AF will be defined as in previous ARIC analyses.[29] Study participants underwent ECG recordings at baseline and at each follow-up exam. All ECG recordings automatically coded as AF were visually re-checked by a trained cardiologist to confirm the diagnosis. A trained abstractor obtained and recorded all ICD-9 hospital discharge diagnoses from each participant's hospitalizations reported in the annual follow-up interview. AF will be defined as the presence of ICD-9-CM code 427.31 or 427.32 or ICD-10-CM I48.x in the discharge codes. AF hospitalization diagnoses occurring simultaneously with heart revascularization surgery or other cardiac surgery involving heart valves or septa, without evidence of AF in subsequent hospitalizations or study exams will be excluded. ARIC participants will be also labeled as AF cases if the

underlying cause of death was AF. The incidence date of AF will be defined as the date for the first ECG showing AF, the first hospital discharge with an AF diagnosis, or date of death for events identified from death certificates exclusively. Follow-up will be available through the end of 2016.

Other Variables of Interest

Demographic – Age, Race, Sex, Education, Height, Weight, Clinic site
Comorbidities – Cigarette smoking, SBP, DBP, Coronary heart disease, Heart failure, Stroke, ECG-based left ventricular hypertrophy[30]
Laboratory data – fasting glucose, TC, LDL, HDL, CRP
Medication use – Anti-hypertensive use, anti-DM use, and anti-depressant use
Others – Alcohol consumption, Physical activity levels

Exclusion criteria

Individuals without at least one exposure variable measured at baseline (defined as visit 2), missing baseline covariate data, with baseline AF, or without follow-up data for AF will be excluded. We will also exclude participants of race other than white or black, and non-whites from the Minneapolis and Washington County sites.

Analysis plan:

Eligible participants not meeting any of the exclusion criteria above will be part of the study analysis.

1) Comparison of baseline characteristics

Descriptive statistics will be computed for all baseline variables. We will examine the distributions of variables by the psychosocial variables of interest

2) Associations of baseline psychosocial measures with incident AF

-Cox proportional hazards models will be used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of each psychosocial measure with incident AF. Person-years will accrue from the participant's visit 2 date to the date of the participant's first AF event, loss to follow-up, death, or end of follow-up, whichever occurred first. Models will be run with the psychosocial measures modeled continuously (per SD increment) and also categorically according to the groupings described above. We will explore non-linear associations using quadratic terms and splines.

-Model 1 will be adjusted for: age, race, sex, education, height, and site

-Model 2 will be adjusted for: Model 1 + weight, cigarette smoking, DM, SBP, DBP, anti-hypertensive medication, TC, HDL, physical activity, alcohol consumption, coronary heart disease, congestive heart failure, left ventricular hypertrophy, and stroke.

-Primary analyses will determine the association of psychosocial measures with incident AF ascertained with each psychosocial measure evaluated in separate models and include covariates from visit 2. Secondary analyses will model the psychosocial measures simultaneously.

-We will evaluate the effect modification by race and sex using a stratification technique and comparing models with and without interaction terms.

- We will test the proportional hazards assumption using adequate tests.

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

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 (This file ICTDER has been distributed to ARIC Pis, and contains the responses to consent updates related to stored sample use for research.)

8. **Will the DNA data be used in this manuscript?**
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
YES

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)?**
The author identifies no significantly related manuscript proposals. Co-authors with extensive ARIC experience for prior proposals related atrial fibrillation have been contacted to collaborate. Other manuscripts related to psychosocial variables and CVD outcomes include:
    - Social isolation, vital exhaustion and incident HF (PMID: 22588323)
    - Vital exhaustion as a risk for CVD events (PMID: 20538111)
    - Anger proneness, gender and risk of HF (PMID: 25284390)

    We have invited Tom Mosley, coauthor in these previous manuscripts, to participate in this proposal.

11. **Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?**
NO

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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