ARIC Manuscript Proposal #2900

PC Reviewed: 12/13/16 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
Resting Heart Rate and Incidence of Atrial fibrillation in the Atherosclerosis Risk in Communities Study cohort

b. Abbreviated Title (Length 26 characters):
Heart Rate & incident AF

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

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3. Timeline:
November 2016 to March 2017

4. Rationale:

Atrial fibrillation (AF) is the most frequent arrhythmia seen in clinical practice. It increases the risk of cardiovascular diseases, particularly stroke and overall mortality[i]. Due to the rising incidence over the past 50 years[ii], the prevalence of AF is projected to double by 2050[iii], underscoring the need for identifying risk factors to predict and prevent this arrhythmia.

The relationship between heart rate in sinus rhythm and the risk of developing AF is not well characterized. Both low and high heart rates have been associated with increased risk of AF in different populations. Low resting heart rate was found to be associated with increased risk of AF in athletes[iv] and participants aged 65 years or more in the Cardiovascular Health Study[v]. Possible mechanisms include underlying alteration in autonomic tone and/or subclinical sinus node dysfunction. On the other hand, high resting in-treatment heart rate was independently associated with an increased risk of AF in hypertensive patients in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study[vi]. High heart rate may represent increased sympathetic activity[vii] and subclinical reductions in LV function[viii] in hypertensive patients. In the Framingham Heart Study, the baseline heart rate between 1983 and 1987 was similar between participants who developed AF and those who remained in sinus rhythm over the next 10 years.[ix]. The differential association between heart rate in sinus rhythm and risk of developing AF calls for further study to confirm previous findings and evaluate potential effect modifiers. In addition, the association between change of heart rate over time and risk of developing AF is unclear.

5. Main Hypothesis/Study Questions

Hypothesis 1: The association between resting heart rate and risk of developing AF is "J"-shaped: both low heart rates and high heart rates are associated with increased risk.

Hypothesis 2: Age modifies the association between resting heart rate and incident AF.

Hypothesis 2a. Low resting heart rate is a stronger risk factor in older populations, as it could be an early sign of sinus node dysfunction.

Hypothesis 2b: High resting heart rate is a stronger risk factor in younger populations, possibly representing poor autonomic function and decreased vagal tone.

Hypothesis 3: The incidence of AF is higher in white individuals than in black individuals despite traditional risk factors being less prevalent in the former[x]. Due to this paradox, we will explore the role of race/center as an effect modifier of the association between heart rate and AF.

Hypothesis 4: The decrease in heart rate over time in participants aged 60 years or older is associated with an increased risk of developing AF, possibly due to progressive sinus node dysfunction.

Hypothesis 5: The increase in heart rate over time in participants aged less than 60 years is associated with an increased risk of developing AF, possibly due to increased sympathetic tone and subclinical reduction in LV 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 population: We will include all 13,500 participants seen at visit 2.
Exclusion criteria:
(1) prevalent AF at baseline;
(2) prevalent sick sinus syndrome, use of pacemaker, bundle branch block, Wolf-Parkinson White syndrome, and idioventricular rhythm;
(3) taking medication known to affect heart rate (beta-blockers, calcium-channel blockers, digoxin and other antiarrhythmics);
(4) being non-white or non-black from all study sites, and non-white from the Minneapolis and Washington County sites;
(5) missing covariates, missing ECG data and poor quality ECG recordings.

Exposure assessment: Heart rates measured from resting 12-lead ECG in visit 2 to visit 5 will be retrieved.

Outcome ascertainment: Atrial fibrillation diagnosis will be identified between visit 2 (1990-1992) and December 31, 2013 from three sources, as previously described[x]: ECGs at 4 visits (visits 2 through 5), hospital discharge records and death certificates. AF is defined as the presence of ICD-9 code 427.31 or 427.32 in the discharge codes. We will exclude AF hospitalization diagnoses occurring simultaneously with heart revascularization surgery (ICD code 36.X) or other cardiac surgery involving heart valves and septa (ICD-9 code 35.X) without evidence of AF in subsequent hospitalization or study exams. If the underlying cause of death was AF (ICD-9 code 427.3) and no AF was documented prior to death, participants will also be considered as AF cases. (Only 3 cases of incident AF were identified on death certificates in ARIC from 1987-2004[x], leaving the potential bias from such ascertainment method minimal.)

The incidence date of AF is defined as the date of the first ECG showing AF, the first hospital discharge with an AF or atrial flutter diagnosis (the latter only if AF was identified later in the same patient) or death by AF, whichever occurred earlier.

The diagnosis of incident AF on hospital discharge has been validated[x]: sensitivity was found to be 84% (African American 80%, white 85%) and specificity, 98% (African American 99%, white 97%).

Covariates measurement

Covariate name	Type	Description	Time of collection
Age	Continuous	Year	Visit 2
Gender	Categorical	Male/female	Visit 1
Race	Categorical	Black/white	Visit 1
Pack-years	Categorical	zero or ≤15/ 15 -35/ >35[xi]	Visit 2
Alcohol consumption	Categorical	current/former/never	Visit 2
Physical activity	Ordinal	Sport score, work score and leisure score[xii] on Baecke Questionnaire	Visit 1 Visit 3
Education	Ordinal	less than high school/ high school degree/ some college/ bachelor's degree and above[xiii]	Visit 1 Visit 2
Income	Ordinal	under $24,000 / $24,000 to $49,999 / $50,000 or more[xiii]	Visit 1 Visit 2
Health insurance	Categorical	insured/ not insured At visits 1, 2, and 3, participants were asked: "Do you have health insurance, such as Medicare, or a medical plan such as an health maintenance organization (HMO) which pays part of a hospital, doctor's or surgeon's bill?" Participants with an affirmative answer to this question were coded as insured at that visit. At visit 4, participants were asked: "To help pay for your medical care, do you now have: (a) health insurance or a health plan, such as Blue Cross/Blue Shield or an HMO, (b) Medicare, (c) Medicaid, (d) other." Any participant that responded with options a, b, or c were designated insured at visit 4. We will decide on option (d) after we see the exact data. [xiv].	Visit 2 Visit 3
Self-reported medication	Categorical	Beta-blocker, calcium channel blocker, digoxin, other antihypertensive medication, antiarrhythmic medications and diabetic medication	Visit 2
Height[xv]	Continuous	cm	Visit 2
Weight	Continuous	kg	Visit 2
Systolic blood pressure	Continuous	mmHg	Visit 2
Diastolic blood pressure	Continuous	mmHg	Visit 2
Presence of hypertension	Categorical	Yes/no (blood pressure of ≥140/90 mm Hg or current use of	Visit 2

		antihypertensive medication)	
Presence of diabetes	Categorical	No/IFG/DM -Impaired fasting glucose : fasting glucose ≥ 100 and <126 mg/dl) -DM: fasting glucose greater than 126 mg/dL, nonfasting glucose 200 mg/dL or more, self-reported physician diagnosis, or pharmacologic hypoglycemic treatment[xvi])	Visit 2
History of myocardial infarction	Categorical	a self-reported history of a physician-diagnosed myocardial infarction or evidence of previous myocardial infarction in the baseline ECG	Visit 2
History of heart failure at baseline	Categorical	yes/no the reported use of heart failure medications in the previous 2 weeks before the visit or the presence of heart failure according to Gothenburg criteria; incident heart failure was defined as the presence of ICD-9-CM code 428 in any hospitalization or death certificate during follow-up[xvii]	Visit 2
Presence of heart failure through the follow-up	Categorical	yes/no Heart failure events are based on (1) annually by phone and interviewed about interim hospitalizations; (2) local hospitals provided lists of hospital discharges (3) health department death certificate files were continuously surveyed (4) death certificates[xviii]. At each visit, prevalent HF was defined as the reported use of HF medication in the previous 2 weeks, the presence of HF according the Gothenburg criteria (only at the baseline visit), or having developed incident HF from the previous visit.	Visit 2 (1990–1992) Visit 3 (1993–1995) Visit 4 (1996–1998) Visit 5 (2011–2013) Annual telephone interviews
Heart rate on ECG	Continuous	Beats per minute	Visit 2 Visit 3 Visit 4 Visit 5
Terminal P negativity in lead V1	Categorical	>4000 μV*ms < 4000 μV*ms	Visit 2
LDLc	Categorical[xix]	<100mg/dL 100-159 mg/dL ≥160 mg/dL	Visit 2

HDLc	Categorical[xix]	<40 mg/dL 40-59 mg/dL ≥60 mg/dL	Visit 2
Triglycerides	Categorical[xx]	<150 mg/dL 150-199 mg/dL ≥200 mg/dL	Visit 2
TSH	Categorical	Hyperthyroidism <0.56 mIU/L High-normal thyroid function 0.56 -1.69mIU/L[xxi] Euthyroidism 1.70 – 5.1mIU/L Hypothyroidism ≥5.1mIU/L *The derived reference ranges of TSH in ARIC were 0.56–5.1 mIU/L for TSH (0.61–5.4 for whites and 0.47–4.2 for blacks)[xxii].	Visit 2
eGFR calculated from blood creatinine	Categorical[xvii]	≥90mL/min/1.73 m2 60-89 mL/min/1.73 m2 30-59 mL/min/1.73 m2 15-30 mL/min/1.73 m2	Visit 2
NT-proBNP	Continuous[xxiii]	pg/dl	Visit 2

Data analysis:

1. Resting heart rate and risk of developing of AF

Incidence rates of AF will be calculated according to resting heart rate in visit 2 from less than 45 beats per minute to more than 90 beats per minute using intervals of 10 beats per minute. (<50 beats per minute, 50-59 beats per minute, 60-69 beats per minute, 70-79 beats per minute, 80-89 beats per minute, 90 -99 beats per minute, >100 beats per minute). Kaplan-Meier survival curves will be used to evaluate survival-free atrial fibrillation.

The relationship between development of AF and heart rate during sinus rhythm on baseline and ECGs will be assessed using Cox proportional hazards models. Person-time will be calculated as the number of years of observation from visit 2 examination to the date of incident atrial fibrillation or censoring (either death, loss to follow-up, or administrative censoring on December 31, 2013). If the incremental change in incidence rate follows a linear pattern with respect to the heart rate change, heart rate change then will be treated as a continuous variable using beats per minute as the analytic unit. We will also examine the graphical association between heart rate and development of AF using a restricted cubic spline model and incorporate knots at the 5th, 50th and 95th percentiles[v].

Model 1 will include age, sex and race. Model 2 will additionally adjust for smoking, alcohol use, physical activity, education, health insurance, height, BMI, presence of hypertension, presence of diabetes, heart rate, history of myocardial infarction, history of heart failure, left ventricular hypertrophy on ECG, p-wave prolongation, PR interval, LDLc, HDLc, triglycerides, TSH, eGFR and NT-proBNP.

We will evaluate stratified associations for interactions by age (48-54 years and 55-67 years), race, prevalent diabetes mellitus and hypertension statuses. Heterogeneity will be tested in the context of the Cox regression models.

2. Heart rate change over time and risk of developing AF

Participants who did not have AF before and at visit 3 will constitute the study population. We will attempt to quantify the heart rate changes between visits 2 and 3 in the following ways:

a. Participants will be categorized into three groups in visit 2 and visit 3:
   - Group 1: high heart rate (>90 beats per minute)
   - Group 2: normal heart rate (60-90 beats per minute)
   - Group 3: low heart rate (<60 beats per minute).

   The change between groups from visit 2 to 3 for each participant will be treated as a categorical variable. Nine categories will be considered (low to high, low and low, etc). This approach is more sensitive in capturing changes when the participant's heart rate is around the cutoffs (60 beats per minute and 90 beats per minute).
b. Heart rate changes will be calculated by subtracting heart rate at visit 2 from heart rate at visit 3. The changes will then be treated as categorical variables:
   - Decrease: change of less than one standard deviation(SD) of the difference between visit 2 and 3
   - Stable: within one SD of the difference between visit 2 and 3
   - Increase: change of more than one SD of the difference between visit 2 and 3.

   We will also perform the analysis using 10 beats per minute as the analytic unit, instead of one SD of the difference. Ten beats per minute is chosen because we consider it as a clinically meaningful change in heart rate.
c. Percentage annual change in heart rate assuming linear change on the log scale will be calculated as [(heart rate at visit 3/heart rate at visit 2) ^ (years elapsed between visit 2 and visit 3)-1] *100. The changes will then be treated as categorical variables:
   Decrease: percentage annual change <-5%/year
   Stable: -5%/year < percentage annual change < 5%/year
   Increase: percentage annual change > 5%/year

The association between incident AF and heart rate change will be examined using Cox regression models. Attempts will be made to control for the effect of baseline heart rate both by adjustment in the Cox model and stratification (by low, medium and high baseline heart rates). Model 1 will include age, sex and race. Model 2 will additionally adjust for smoking, alcohol use, physical activity, education, health insurance status, height, BMI, presence of hypertension, presence of diabetes, heart rate at visit 1, history of myocardial infarction, history of heart failure, left ventricular hypertrophy on ECG, p-wave prolongation, PR interval in visit 1, LDLc, HDLc, triglycerides, TSH, eGFR and NT-proBNP.

We will also evaluate interactions by age (48-59 years and 60-67 years) using stratification and Cox regression models.

Anticipated methodologic limitations or challenges

Paroxysmal atrial fibrillation is likely to be underestimated with the three sources of ascertainment used in our analysis.

Echocardiography data are not available in ARIC before visit 5. We will not be able to assess left atrial enlargement and mitral valve pathology accurately.

Residual confounding is always an issue in observational studies despite the adjustment of multiple variables.

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/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)?

- Alonso, Alvaro, et al. "Incidence of atrial fibrillation in whites and African-Americans: The Atherosclerosis Risk in Communities (ARIC) study." American heart journal 158.1 (2009): 111-117.
- Sunil K. Agarwal et al. Cardiac Autonomic Dysfunction and Incidence of Atrial Fibrillation in a Large Population Based Cohort". JACC 2016 in press.

* Drs. Alvaro Alonso and Elsayed Soliman agreed to be co-authors.

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

___ A. primarily the result of an ancillary study (list number* _____)
__x_ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____)

number	Name	Variable
2009.24	**Subclinical thyroid dysfunction and clinical outcomes**	**TSH at visit 2**
2009.16	**BNP**	**N-proBNP at visit 2[xxiv]**

*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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __x__ No.

References

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v O'NEAL, WESLEY T., Mohamed F. Almahmoud, and Elsayed Z. Soliman. "Resting heart rate and incident atrial fibrillation in the elderly." Pacing and Clinical Electrophysiology 38.5 (2015): 591-597.

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x Alonso, Alvaro, et al. "Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study." American heart journal 158.1 (2009): 111-117.

xi Chamberlain, Alanna M., et al. "Smoking and incidence of atrial fibrillation: results from the Atherosclerosis Risk in Communities (ARIC) study." Heart Rhythm 8.8 (2011): 1160-1166.

xii Mozaffarian, Dariush, et al. "Physical activity and incidence of atrial fibrillation in older adults the cardiovascular health study." Circulation 118.8 (2008): 800-807.

xiii Chichlowska, Kristal L., et al. "Individual and Neighborhood Socioeconomic Status Characteristics and Prevalence of Metabolic Syndrome. The Atherosclerosis Risk in Communities (ARIC) Study." Psychosomatic medicine70.9 (2008): 986.

xiv Fowler-Brown, Angela, et al. "Risk of cardiovascular events and death—does insurance matter?." Journal of general internal medicine 22.4 (2007): 502-507.

xv Rosenberg, Michael A., et al. "The impact of height on the risk of atrial fibrillation: The Cardiovascular Health Study." European heart journal 33.21 (2012): 2709-2717.

xvi Schroeder, Emily B., et al. "Diabetes, glucose, insulin, and heart rate variability the atherosclerosis risk in communities (ARIC) study." Diabetes care 28.3 (2005): 668-674.

xvii Alonso, Alvaro, et al. "Chronic Kidney Disease Is Associated with the Incidence of Atrial Fibrillation the Atherosclerosis Risk in Communities (ARIC) Study." Circulation 123.25 (2011): 2946-2953.

xviii Loehr, Laura R., et al. "Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study)." The American journal of cardiology 101.7 (2008): 1016-1022.

xix Lopez, Faye L., et al. "Blood Lipid Levels, Lipid-Lowering Medications, and the Incidence of Atrial Fibrillation The Atherosclerosis Risk in Communities Study." Circulation: Arrhythmia and Electrophysiology 5.1 (2012): 155-162.

xx Alonso, Alvaro, et al. "Blood lipids and the incidence of atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis and the Framingham Heart Study." Journal of the American Heart Association 3.5 (2014): e001211.

xxi Heeringa, Jan, et al. "High-normal thyroid function and risk of atrial fibrillation: the Rotterdam study." Archives of Internal Medicine 168.20 (2008): 2219-2224.

xxii Schultheiss, Ulla T., et al. "Thyroid function, reduced kidney function and incident chronic kidney disease in a community-based population: the Atherosclerosis Risk in Communities study." Nephrology Dialysis Transplantation (2016): gfw301.

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xxiv Ndumele, Chiadi E., et al. "NT-proBNP and heart failure risk among individuals with and without obesity: The ARIC study." Circulation (2016): CIRCULATIONAHA-115.