ARIC Manuscript Proposal # 3289

PC Reviewed: 12/11/18 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Resting Heart Rate and Incidence of Venous Thromboembolism (VTE)

b. Abbreviated Title (Length 26 characters): Heart rate and VTE

2. Writing Group:
Writing group members: Aaron Folsom, Pam Lutsey, Oluwaseun Fashanu, Mary Cushman, Erin Michos

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _____ **[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).
Name:
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Phone: Fax:
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3. Timeline: Winter 2019

4. Rationale:

Higher resting heart rate is a marker of poor physical fitness. Yet, even after accounting for fitness, higher heart rate is consistently associated with elevated arterial cardiovascular disease risk, total mortality risk, higher blood pressure, and higher inflammatory markers (1-4). The MESA study recently presented data showing a high resting heart rate is a risk factor for VTE (deep vein thrombosis and pulmonary embolism) (5). VTE risk was twice as high in those with heart rate >80 vs <60. MESA defined VTE by unvalidated ICD discharge codes.

There appear to be no other publications addressing heart rate and VTE. The mechanisms for a VTE association are speculative but include a systemic effect of excessive sympathetic to parasympathetic activity; residual confounding from low physical fitness, obesity/metabolic syndrome, or other cardiovascular diseases; inflammation; or possible effects on sheer stress/stasis or hemostasis. However, most of these possible mechanisms are more relevant to arterial disease than venous thrombosis.

We would like to examine this association in ARIC, using VTEs validated by our Longitudinal Investigation of Thromboembolism Etiology (LITE).

References:

1. Perret-Guillaume C, Joly L, Benetos A. Heart rate as a risk factor for cardiovascular disease. Prog Cardiovasc Dis. 2009 Jul-Aug;52(1):6-10.
2. Aladin AI, Al Rifai M, Rasool SH, Keteyian SJ, Brawner CA, Michos ED, Blaha MJ, Al-Mallah MH, McEvoy JW. The Association of Resting Heart Rate and Incident Hypertension: The Henry Ford Hospital Exercise Testing (FIT) Project. Am J Hypertens. 2016 Feb;29(2):251-7.
3. Aladin AI, Whelton SP, Al-Mallah MH, Blaha MJ, Keteyian SJ, Juraschek SP, Rubin J, Brawner CA, Michos ED. Relation of resting heart rate to risk for all-cause mortality by gender after considering exercise capacity (the Henry Ford exercise testing project). Am J Cardiol. 2014 Dec 1;114(11):1701-6.
4. Whelton SP, Narla V, Blaha MJ, Nasir K, Blumenthal RS, Jenny NS, Al-Mallah MH,Michos ED. Association between resting heart rate and inflammatory biomarkers (high-sensitivity C-reactive protein, interleukin-6, and fibrinogen) (from the Multi-Ethnic Study of Atherosclerosis). Am J Cardiol. 2014 Feb 15;113(4):644-9.
5. Awotoye J, Fashanu OE, Lutsey PL, Zhao D, O'Neal WT, Michos ED. Abstract 12782: Elevated Resting Heart Rate is Associated With the Incidence of Venous Thromboembolism: The Multi-Ethnic Study of Atherosclerosis. Circulation 2018;138:A12782-A12782.

5. Main Hypothesis/Study Questions: Is heart rate at baseline or as a time dependent variable a risk factor for VTE?

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).

Design: prospective starting at visit 1
Exclusions (visit 1): missing heart rate, prevalent VTE, anticoagulant use
Exposure: visit 1 heart rate from ECG; secondary analysis—heart rate at every visit
Outcome: incident validated VTE (leg DVT or PE) through 2015 (n of VTEs >700). Subsets are: DVT and PE separately, provoked and unprovoked
Covariates (visit 1): age, race, sex, BMI, diabetes, cigarette smoking, sports score, AV nodal blocking medications (beta-blockers, calcium channel blockers, digoxin, amiodarone), eGFR, von Willebrand factor, factor VIII, VTE 5-snp genetic risk score (GRS).

Analysis:

1. Examine covariates by V1 heart rate categories (<=60, 60-69, 70-79, 80+ bpm in MESA)
2. Calculate incidence rates by V1 heart rate categories. Kaplan-Meier graphs.
3. Using Cox models, test proportional hazards assumption and estimate hazard ratios by V1 heart rate categories and by continuous heart rate
   Model 1: adjusted for age, race, sex (after verifying none of these interacts with heart rate).

Model 2: also adjusted for BMI, diabetes, smoking, sports score, eGFR, AV nodal blocking medications
Model 3: also adjusted for von Willebrand factor, factor VIII
Examine in Model 2 or 3 effect modification by GRS, using stratification and cross-product terms.

4. Sensitivity analysis, using time-dependent heart rate and Model 1 covariates and repeated with Model 2 covariates but making AV nodal meds time-dependent as well.

Heart rate is correlated moderately with heart rate variability. In an exploratory analysis, we will also examine the association of incident VTE with heart rate variability indices from the 2-minute rhythm strip at Visit 1. Indices include: the SD of RR intervals [SDNN], the root mean square of successive differences of successive RR intervals, the mean of all normal RR intervals [mean NN], low-frequency [LF] and high frequency [HF] power, and the LF/HF ratio.

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? __x__ Yes ____ 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"? __x__ 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)?

All related proposals are ours.

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* __2001.16__)
___ 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/

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.