**ARIC Manuscript Proposal #2677**

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| **PC Reviewed: 12/8/15** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: **Premature Ectopic Beats on the 10-second Electrocardiogram as Predictors of Incident Atrial Fibrillation and Heart Failure**

**b. Abbreviated Title (Length 26 characters)**: **12-lead ectopy, AF, and HF**

**2. Writing Group**:

Writing group members: Kaylin Nguyen, Elsayed Soliman, Thomas Dewland, Jonathan Dukes, Alvaro Alonso, Lin Y. Chen, Eric Vittinghoff, Bruce Psaty, Susan R. Heckbert, Gregory M. Marcus

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

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**3. Timeline**:

Dr. Marcus has the majority of this data available from previously approved manuscript proposals and grant funding. Kaylin Nguyen, the first author, is a medical student at UCSF on a yearlong pre-doctoral clinical and translational research grant, simultaneously taking classes in epidemiology and biostatistics. As such, she should have sufficient time and support from Dr. Marcus and the biostatistics department at UCSF to complete this project within six months from its approval. In addition, we already have

certification from the UCSF Committee on Human Research to perform this study, as they do not require specific approval to analyze de-identified data.

**4. Rationale**:

Premature ectopic beats detected on the 12-lead electrocardiogram (ECGs) are common in middle-aged and older adults.[1, 2]

PAC count is an independent predictor of atrial fibrillation (AF), stroke, and mortality.[3, 4] PACs have been shown to be critical to AF pathophysiology[5, 6] and our group has shown that PAC count alone was at least as predictive of AF risk as a validated, multivariable Framingham risk model.[3] The presence of PACs on the standard 12-lead ECG has been associated with all-cause mortality, cardiovascular mortality and ischemic heart disease mortality,[7] suggesting that the association between PACs and adverse outcomes can be studied using measurements from the 10-second ECG recording. However, the association between the presence of PACs on the standard (10-second) 12-lead ECG and incident AF is unknown.

Premature ventricular contractions (PVCs) are common and associated with older age, race, and heart disease.[2] In otherwise healthy adults, high burden ventricular contractions (PVCs) have conventionally been considered benign.[8] However, recent studies have found that PVC count is a predictor of incident heart failure and mortality.[9, 10] The presence of ≥ 1 PVCs on the 2-minute rhythm strip has been shown to be a predictor of incident heart failure, coronary heart disease, and mortality.[11, 12] Additionally, the presence of PVCs on the 10-second ECG recording has been associated with all-cause and cardiovascular mortality.[13] These studies suggest that shorter recordings can be used to accurately detect the association between PVCs and adverse outcomes, such as heart failure.

The standard 10-second 12-lead ECG is a widely used tool that is more readily available than longer recordings. If relationships between a PAC and AF or PVC and HF obtained from such a 12-lead ECG exist, understanding the strength of that relationship and the specific utility of the 12-lead ECG as a predictor of these important diseases could have important clinical ramifications.

**5. Main Hypothesis/Study Questions**:

- Aim 1: To determine whether the presence of at least one PAC on the standard 10-second, 12-lead ECG is associated with incident atrial fibrillation.
- Aim 2: To determine whether the presence of at least one PVC on the standard 10-second, 12-lead ECG is associated with incident heart failure.

**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).**

Dr. Marcus has the majority of this data available from previously approved manuscript proposals and grant funding. The only additional data needed are presence of at least one PAC or PVC on each serial 12-lead ECG.

We plan to measure the presence of one or more PACs on the 10-second, 12-lead ECG as a predictor of incident AF and one or more PVCs on the 10-second, 12-lead ECG as a predictor of incident heart failure. The primary analysis will examine the presence of

ectopic beats on the baseline ECG as a predictors of incident events. In secondary analyses, we will examine serial ECGs to analyze the association between the presence of ectopic beats on multiple ECGs and the outcomes of interest.

T-tests or ANOVA will be used to compare normally distributed continuous data and nonparametric tests will be used for continuous data that is not normally distributed. Chi squared tests will be used to compare categorical data. The predictors will be dichotomized into the presence or absence of any PAC or PVC on ECG. In the PAC and AF analysis, we will exclude participants with prevalent AF. In the PVC and CHF analysis, we will exclude participants with prevalent CHF, and, among participants with echocardiography data available, abnormal left ventricular ejection fraction (a second related proposal is being submitted to the Jackson Heart Study to obtain echocardiographic data). The primary analyses will be performed using survival analyses with multivariable Cox Proportional Hazards models, with the repeated measures of PACs and PVCs as time-dependent covariates. Potential confounders at baseline and as time-dependent covariates will be included in these models and will include age, race, body mass index, hypertension, diabetes, coronary disease, MI, AF (in the heart failure analysis) and heart failure (in the AF analysis).

With the assistance of Dr. Elsayed Soliman, we have already determined that 218 participants had PACs and 279 participants had PVCs on baseline ECG, 1424 participants had PACs and 1170 participants had PVCs on any visit ECG, and 1073 participants had PACs and 978 participants had PVCs on an ECG from visits 1-4 (which is relevant because the 5$^{th}$ and most recent visit was completed only a few years ago, precluding longer follow-up time). For analyses of a PAC as a predictor of AF restricted to the baseline ECG (given that 1.4% have at least one PAC and approximately 10% develop incident AF), we estimate that we have 80% power to detect a statistically significant hazard ratio as small as 1.89; if ECGs 1-4 are used (where 7% of participants have exhibited at least one PAC), we will have 80% power to detect a statistically significant hazard ratio as low as 1.34. Similarly, for analyses of a PVC as a predictor of HF restricted to the baseline ECG (given that 2% have at least one PVC and assuming approximately 10% will develop incident HF), we estimate that we have 80% power to detect a statistically significant hazard ratio as small as 1.70; if ECGs 1-4 are used (where 6.5% of participants have exhibited at least one PVC), we will have 80% power to detect a statistically significant hazard ratio as low as 1.35.

**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)?**

- [946] Agarwal SK, Simpson RJ, Rautaharju P, Alonso A, Shahar E, Massing M, Saba S, Heiss G. 2012. Relation of ventricular premature complexes to heart failure (from the Atherosclerosis Risk In Communities [ARIC] Study). Am J Cardiol. 109(1):105-9.*
  ***The 2-minute rhythm strip was utilized for the above paper while the 10-second 12 lead will be used for the current proposal. Additionally, authors from the above paper are already included in the current proposal.**

- Agarwal SK, et al. Premature ventricular complexes and the risk of incident stroke: the Atherosclerosis Risk In Communities (ARIC) Study. Stroke. 2010 Apr;41(4):588-93.

**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/

**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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