ARIC Manuscript Proposal #4364

PC Reviewed: 11/21/23 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:

Premature Ventricular Contraction Location and Incident Heart Failure

b. Abbreviated Title (Length 26 characters):

PVCs and HF

2. Writing Group:

Thomas A. Dewland, MD	thomas.dewland@ucsf.edu
David G. Rosenthal, MD	david.rosenthal@ucsf.edu
Gregory M. Marcus, MD, MAS	greg.marcus@ucsf.edu
Alvaro Alonso, MD, PhD	alvaro.alonso@emory.edu
Elsayed Soliman, MD, MS	esoliman@wakehealth.edu
Lin Chen, MD, MS	chenx484@umn.edu
Edward Gerstenfeld, MD	edward.gerstenfeld@ucsf.edu
Melvin Scheinman, MD	melvin.scheinman@ucsf.edu
David Siscovick, MD, MPH	dsiscovick@nyam.org
Nona Sotoodehnia, MD	nsotoo@uw.edu
John Gottdiener, MD	jgottdie@medicine.umaryland.edu
Bruce Psaty, MD, PhD	psaty@uw.edu
Susan Heckbert, MD, PhD	heckbert@uw.edu
Phyllis K. Stein, PhD	pstein@wustl.edu

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

First author:	Thomas A. Dewland, MD
Address:	500 Parnassus Ave Millberry Union East 431 San Francisco, CA 94143
Phone:	(415) 476-5706
Fax:	(415) 502-4545
E-mail:	thomas.dewland@ucsf.edu
Corresponding author:	Gregory M. Marcus, MD, MAS
Address:	500 Parnassus Ave

	Millberry Union East 431 San Francisco, CA 94143
Phone:	(415) 476-5706
Fax:	(415) 502-4545
E-mail:	greg.marcus@ucsf.edu

ARIC author:	Elsayed Z. Soliman, MD, MS
Address:	5213 Medical Center Blvd. Winston-Salem, NC 27157-1063
Phone:	(336) 716-8632
Fax:	(336) 716-0834
E-mail:	esoliman@wakehealth.edu

3. Timeline:

The analysis and manuscript will be completed within 6 months of approval.

4. Rationale:

This is a manuscript proposal for the previously approved ARIC Ancillary Study 2015.25 "Characteristics of Ectopy Most Strongly Associated with Chamber-Specific Cardiac Myopathy."

Our research group has previously demonstrated that premature ventricular contraction (PVC) frequency is an important, independent risk factor for the development of incident heart failure (HF).[1,2] However, it is unknown if all PVCs equally contribute to cardiomyopathy risk or whether PVCs arising from certain locations within the right or left ventricle differentially impact the likelihood of incident HF. Furthermore, the overall distribution of PVC anatomic site of origin in a general population of community dwelling adults remains entirely unknown.

5. Main Hypothesis/Study Questions:

The primary aim of this study is to identify whether PVC anatomic site of origin, as assessed by 12-lead electrocardiogram (ECG) morphology, is associated with incident HF. We hypothesize that PVCs arising from the free wall (lateral right ventricle or lateral left ventricle) result in greater risk of HF through enhanced electrical and mechanical ventricular dyssynchrony.

We will evaluate whether PVC ECG characteristics are associated with incident HF after accounting for potential clinical confounders.

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).

This analysis will include all ARIC participants with a baseline ECG (with and without a PVC). The primary outcome with be a diagnosis of incident heart failure. Subject demographics, including age, gender, race, body mass index, and history of hypertension, diabetes, myocardial infarction, coronary artery disease, and heart failure, will be recorded.

The following PVC characteristics will be determined from expert analysis of baseline 12-lead ECGs:

1. PVC anatomic site of origin
2. PVC coupling interval (time in milliseconds from prior sinus beat to PVC initiation)
3. PVC duration
4. Total number of PVCs on 12 lead ECG
5. Number of distinct PVC morphologies noted

All 12-lead ECGs will be independently analyzed by two board-certified attending cardiac electrophysiologists (EPG, MS). When required, a third board-certified cardiac electrophysiologist (GMM) will adjudicate discrepant interpretations.

The association between each PVC characteristic and incident HF will be determined using Cox proportional hazards models both before and after adjusting for potential confounders, including age, gender, race, body mass index, and history of hypertension, diabetes, myocardial infarction, coronary artery disease. Participants with baseline heart failure will be excluded from incident analyses.

All PVC characteristics associated with incident HF in adjusted models will be included in a final Cox model to determine which characteristics are independently associated with HF.

The primary analysis will examine the association between PVC anatomic location and incident heart failure. In these analyses, participants with ventricular ectopy arising from a single generalized anatomic location (e.g. left ventricle) will be compared to individuals without ventricular ectopy on the baseline ECG; participants with baseline ventricular ectopy outside of the anatomic location of interest will be excluded. In a secondary analysis, incident heart failure risk will be compared between participants with ventricular ectopy arising from a given anatomic location and all remaining participants with ventricular ectopy from other locations; individuals without baseline ectopy will be excluded.

The results of the ARIC analysis will be validated using a similar analytic approach among participants enrolled in the Cardiovascular Health Study (CHS) cohort.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript?

XX No

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

XX 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

   The above website is password protected and we are unable to access. However, because this manuscript proposal is directly related to a previously approved ARIC Ancillary Study (2015.25), we do not believe there is any overlap with other investigations. We have included several ARIC investigators/authors in our study and manuscript proposals.

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)?

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11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

XX Yes

This is a manuscript proposal for the previously approved ARIC Ancillary Study 2015.25 “Characteristics of Ectopy Most Strongly Associated with Chamber-Specific Cardiac Myopathy.”

11.b. If yes, is the proposal

XXX **A. primarily the result of an ancillary study (list number*** 2015.25**)**

___ **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 https://sites.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.

References

1. Stein PK, Gottdiener JS, Alonso A, et al. Ectopy on a Single 12-Lead ECG, Incident Cardiac Myopathy, and Death in the Community. *J Am Heart Assoc*. 2017;6(8):e006028. doi:10.1161/JAHA.117.006028
2. Dukes JW, Dewland TA, Vittinghoff E, et al. Ventricular Ectopy as a Predictor of Heart Failure and Death. *J Am Coll Cardiol*. 2015;66(2):101-109. doi:10.1016/j.jacc.2015.04.062