

ARIC Manuscript Proposal # 1555

PC Reviewed: 10/13/09
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Priority: 2
Priority: _____

1.a. Full Title: Premature ventricular contractions and risk of incident HF: The ARIC Study

b. Abbreviated Title (Length 26 characters): PVCs and HF

2. Writing Group: Sunil Kumar Agarwal, Ross J. Simpson, Pentti M. Rautaharju, Mark Massing, Eyal Shahar

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

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3. Timeline:

PVCs have been coded using 2 minutes ECG at ARIC baseline. Manuscript writing will be completed within 15 months of its approval and data release.

4. Rationale:

Premature Ventricular Contractions (PVCs) are common, yet, mostly asymptomatic irregular rhythms seen in electrocardiograms (ECGs). With the exception of patients who have established coronary heart disease, in whom PVCs are considered a marker of disease severity, clinical studies have reported their benign prognosis [1-3]. In contrast to the above, population based studies have consistently shown positive association between PVCs and new onset coronary heart disease (CHD) events [4-7].

PVCs are associated with traditional risk factors for atherosclerosis. Thus, in individuals with PVCs, atherosclerosis likely is a dominant factor for increased cardiac end-points and cardiac specific mortality. If this is so, we expect to see increased HF too in individuals with PVCs.

Another possible mechanism relating to HF is PVCs induced cardiomyopathy. Few case reports and case series have alluded to the existence of PVC induced cardiomyopathy including its reversal with ablation [8-13]. Various sources of origin for PVCs have been implicated including scar tissue[14], papillary muscle[15, 16], Purkinje network system[17],

mitral annulus[18, 19], and aortic sinus cusp[20]; however, it seems that most of the monomorphic and potentially reversible PVCs may originate from the ventricular outflow tract [21].

At the basic electrophysiological level, conditions causing dyssynchrony such as even transient bundle branch blocks have a profound effect on ventricular repolarization, changing action potential duration gradients, and possibly ventricular dimensions and function. A recent study suggested slightly increased chances of left ventricular dysfunction among individuals with no CVD symptoms and normal ejection fraction among those with frequent PVCs (of left ventricular outflow tract origin) during an average follow up of 5.6 years [22]. Similarly, among asymptomatic children, the average ejection fraction and cardiac output was markedly reduced in the presence of PVCs (especially when frequent, or had a short coupling interval, or a prolonged QT interval)[23]. Also, PVCs (of right ventricular outflow tract origin) were associated with impaired left ventricular relaxation [24]. Interestingly, responders of cardiac resynchronization therapy (CRT) had a lower prevalence of PVCs [25] – suggesting their role in continuing decline of function or ill effect on electro-mechanical synchrony. Also, PVCs even when seen during childhood may not be transient and have a continued occurrence especially when associated with left bundle branch block [26].

It remains to be studied whether frequent PVCs are associated with incident heart failure when stratified/adjusted for the other clinically relevant determinants of heart failure (CHD, LVH, heart rate, non-dipolar voltage in women etc). The ARIC study provides an excellent opportunity to study the above in a large bi-ethnic population based cohort.

To summarize, PVCs are common, yet asymptomatic ectopic complexes seen in EKG shown to be associated with CHD and its traditional risk factors. Recent studies point to their potential role in cardiomyopathy. This is suggested by a reduction in ejection fraction and poor diastolic function among those with high frequency PVCs and reversal of cardiomyopathy following their ablation in selected cases. This study will test the association of PVCs and incident HF in the ARIC cohort. The interaction effect due to CHD, LVH, and heart rate will also be explored (the power to test interactions will be limited). Lastly, it will explore whether appearance of PVCs during the baseline visit is associated with prolonged ventricular repolarization during visit 4.

5. Main Hypothesis/Study Questions:

- I. Ventricular premature contractions at baseline are associated with risk of heart failure through 2005
 - a. These associations are seen across gender and race.
 - b. The association between frequency of PVCs and HF is stronger with higher frequency of PVCs.
 - c. The association of PVCs with risk of HF is modified by left ventricular mass / hypertrophy, and heart rate.
- II. PVCs at baseline visit are associated with prolongation of ventricular repolarization as measured by corrected QT interval at subsequent visits.

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 methodological limitations or challenges if present).

Study design: Longitudinal data analysis using Cox regression will be employed. Individuals with a positive or unknown history of HF at the ARIC cohort baseline will be excluded from the analysis (Gothenburg criteria = 3 or intake of HF medications). Also, subjects with race other than African American or Caucasians (n=48) will be excluded. Additionally, patients with cardiac abnormal rhythm such as atrial fibrillation/flutter, WPW syndrome will be excluded.

Cox regression models will be fit to find if there is any difference in the hazards HF comparing those with PVCs to those without in the strata of race, gender, prevalent CHD disease, prevalent ventricular hypertrophy, and heart rate. Measures of associations will be reported separately for two or more stratum (if effect is found heterogeneous in the stratum or more of the above covariate) after adjusting for important confounders. Dose-response will be evaluated by creating strata of increasing frequency of PVCs (single, two – three, more than three). Proportionality hazard assumption and linearity assumption (dose-response) will be examined. Proportional hazard assumption and linearity assumption on PVCs staging will be assessed and appropriate measures taken, if assumptions fails.

Lastly, a linear multivariable model adjusted for age, gender, race, left ventricular mass, and baseline QTc will be fit to test whether prevalent PVCs are associated with QTc measured during repeat visits – stratified by CHD status.

Variables:

ARIC visit 1:

Main exposure : Presence of any PVCs on a two minute rhythm strip ECG

Covariates: Demographics (Age, Race, Gender, Education); Prevalent CHD, Diabetes mellitus, Hypertension, Cholesterol levels (HDL and LDL), ECG abnormality (Atrial Fibrillation/ flutter, Wolf Parkinson White, Wandering atrial pacemaker, supra-ventricular tachycardia); Pharmacotherapy (Angiotensin converting enzyme inhibitors, calcium channel blockers, beta blockers, diuretic, other anti-hypertensive drugs, Digoxin); Serum potassium; Serum Magnesium; Heart rate and Ventricular hypertrophy (Cornell voltage), prevalent HF (Gothenburg criteria = 3 or intake of medications for HF), QTc during visit 1.

Study outcome

Incident HF (hospitalization and deaths) through 2005 identified through ICD discharge codes; QTc at visit 2, visit 3, and visit 4.

7.a. Will the data be used for non-CVD analysis in this manuscript? No

b. NA

8.a. Will the DNA data be used in this manuscript? No

8.b. NA

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.

No overlaps found.

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)?

ARIC proposal #839: PVCs, CHD, and Mortality

ARIC proposal #1378 PVCs, SCD, and Stroke

Authors of above manuscripts are collaborating in writing of this manuscript.

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

11.b. NA

12. 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.

Agreed

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