# ARIC Manuscript Proposal #1378

**PC Reviewed: 06/10/08** **Status: A** **Priority: 2**
**SC Reviewed: _____** **Status: _____** **Priority: ____**

**1.a. Full Title**: Ventricular premature contractions and risk of incident stroke and sudden cardiac death.

**b. Abbreviated Title (Length 26 characters)**: VPCs, Stroke and SCD

**2. Writing Group**: Sunil Kumar Agarwal,
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _SKA__

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**3. Timeline**:
VPCs 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**:
Ventricular Premature Contractions (VPCs) are common, yet, mostly asymptomatic irregular rhythms seen in electrocardiograms (EKGs).

VPCs have a reported prevalence of 6.2%, using 2 minutes rhythm strip at baseline (mean cohort age = 55 years), in the ARIC cohort [1]. With the exception of patients who have established coronary heart disease, in whom VPCs are considered a marker of disease severity, clinical studies have reported their benign prognosis [2-4]. In contrast to the above, population based studies - including a study from the ARIC cohort [5] - have consistently shown positive association between VPCs and coronary heart disease (CHD) events [6-8]. Furthermore, studies using intracardiac EKGs (stored) in patients with an implantable cardioverter defibrillator have consistently shown VPCs as predictors of arrhythmic events [9, 10].

However, in patients with CHD, adverse cardiac events increased following VPCs suppression using class I antiarrhythmic medications (CAST I and II trials). This raised a question about the modifiability of VPCs as a risk factor. Nonetheless, they could play an important role in risk stratification and thus guide aggressive management of other modifiable risk factors associated with them and with CVD events. In this study, our first aim is to explore the association between VPCs and incident stroke.

VPCs are associated with traditional risk factors for atherosclerosis. Thus, in individuals with VPCs, atherosclerosis likely remains a dominant factor for increased cardiac end-points and cardiac specific mortality. If this is so, we expect to see increased stroke too in individuals with VPCs. Another possible mechanism relating to atherothrombotic end points is VPCs mediated arrhythmia.

To our knowledge, only one study published by Engstrom G et. al. has looked at the association between stroke and VPCs (Lown criteria >2). It found an increased rate of stroke with VPCs but these results did not achieve statistical significance [11]. Despite the study's strength of utilizing a 24 hour Holter record to monitor premature contractions, this study had a small sample size and included only males of mostly Caucasian origin [11]. The large sample size of the ARIC cohort, inclusion of African American examinees, and the sizeable number of incident stroke events (525/13875) [12, 13] allows us to explore this relationship further with greater power.

Left ventricular hypertrophy (LVH) measured using echocardiography has been shown to be a predictor of stroke [14]. Similar conclusions were drawn from studies employing LVH measured by ECG [15]. Interestingly, a study of the long term prognosis of VPCs in individuals with ventricular hypertrophy also found an increased rate of all cause mortality (not reaching statistical significance) but not cardiovascular specific mortality [16]. The above findings suggest that VPCs may be a marker of a pathology other than increased blood pressure or hypertensive cardiomyopathy. Whether there are more stroke events in those with VPCs and LVH (or hypertension) as compared to only LVH (or hypertension) remains to be explored, although statistical power to detect such interaction(s) would be relatively limited.

A recent article reported the interaction of VPCs and increased heart rate in predicting all-cause and CVD specific mortality [17]. Increased sympathetic activity has been implicated for the above association [18, 19]. We wish to explore similar interaction of VPCs and increase heart rate with incident stroke as outcome in the ARIC cohort.

To summarize, VPCs are common, yet asymptomatic beats seen in EKG. These have been shown to be associated with coronary heart disease and traditional risk factors. This study will explore the association of VPCs and incident stroke. Also, it will consider the interaction effect due to LVH and increase heart rate. Further, two mechanism outlined above for stroke i.e atherosclerosis and arrhythmogenic potential may also be contributory to sudden cardiac death (SCD). Though, overall CHD mortality has been studied [5], but SCD remains unstudied in ARIC cohort as a outcome following VPCs. Studies done in 90's have reported high risk ratio of SCD as compared to non-SCD in those with VPCs at baseline [6]. We wish to extend the analysis by including SCD as one of the outcomes.

5. Main Hypothesis/Study Questions:
    I. Ventricular premature contractions are associated with risk of incident stroke
        a. These associations are seen across gender and race.
        b. The association of VPCs with risk of stroke and CVD mortality is modified by left ventricular mass / hypertrophy and heart rate.

    II. Ventricular premature contractions are associated with risk of incident sudden cardiac death.

**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 stoke at the ARIC cohort baseline will be excluded from the analysis. 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 association between VPC and stoke (stroke related mortality) 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. Proportionality hazard assumption and linearity assumption (dose-response) will be examined.

Further, Cox regression models will be used to examine the association between VPCs and SCD in the stratum of modifiers after adjusting for important confounders. Proportional hazard assumption and linearity assumption on VPC staging with be assessed and appropriate measures taken, if assumptions fails.

**Variables:**
**ARIC visit 1:**
**Main exposure:** VPCs (Lown's classification).

**Covariates:** Demographics (Age, Race, Gender, Education); Prevalent diseases (stroke, 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)

**ARIC follow up visit (through 2001 or later)**
Stroke (with type); Stroke related death; Sudden Cardiac Death.

**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: Authors of this manuscript 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**

## References:

[1] Simpson RJ, Jr., Cascio WE, Schreiner PJ, Crow RS, Rautaharju PM, Heiss G. Prevalence of premature ventricular contractions in a population of African American and white men and women: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J. 2002 Mar;143(3):535-40.
[2] Kennedy HL, Whitlock JA, Sprague MK, Kennedy LJ, Buckingham TA, Goldberg RJ. Long-term follow-up of asymptomatic healthy subjects with frequent and complex ventricular ectopy. N Engl J Med. 1985 Jan 24;312(4):193-7.
[3] Kostis JB, Lacy CR, Shindler DM, Borhani NO, Hall WD, Wilson AC, et al. Frequency of ventricular ectopic activity in isolated systolic systemic hypertension. Am J Cardiol. 1992 Feb 15;69(5):557-9.
[4] Waldo AL, Biblo LA, Carlson MD. Ventricular arrhythmias in perspective: a current view. Am Heart J. 1992 Apr;123(4 Pt 2):1140-7.
[5] Massing MW, Simpson RJ, Jr., Rautaharju PM, Schreiner PJ, Crow R, Heiss G. Usefulness of ventricular premature complexes to predict coronary heart disease events and mortality (from the Atherosclerosis Risk In Communities cohort). Am J Cardiol. 2006 Dec 15;98(12):1609-12.
[6] Abdalla IS, Prineas RJ, Neaton JD, Jacobs DR, Jr., Crow RS. Relation between ventricular premature complexes and sudden cardiac death in apparently healthy men. The American journal of cardiology. 1987 Nov 1;60(13):1036-42.
[7] Bikkina M, Larson MG, Levy D. Prognostic implications of asymptomatic ventricular arrhythmias: the Framingham Heart Study. Ann Intern Med. 1992 Dec 15;117(12):990-6.
[8] Engel G, Cho S, Ghayoumi A, Yamazaki T, Chun S, Fearon WF, et al. Prognostic significance of PVCs and resting heart rate. Ann Noninvasive Electrocardiol. 2007 Apr;12(2):121-9.
[9] Carrim ZI, Khan AA. Mean frequency of premature ventricular complexes as predictor of malignant ventricular arrhythmias. Mt Sinai J Med. 2005 Nov;72(6):374-80.
[10] Meyerfeldt U, Schirdewan A, Wiedemann M, Schutt H, Zimmerman F, Luft FC, et al. The mode of onset of ventricular tachycardia. A patient-specific phenomenon. Eur Heart J. 1997 Dec;18(12):1956-65.
[11] Engstrom G, Hedblad B, Juul-Moller S, Tyden P, Janzon L. Cardiac arrhythmias and stroke: increased risk in men with high frequency of atrial ectopic beats. Stroke. 2000 Dec;31(12):2925-9.
[12] Volcik KA, Ballantyne CM, Coresh J, Folsom AR, Boerwinkle E. Specific P-selectin and P-selectin glycoprotein ligand-1 genotypes/haplotypes are associated with risk of incident CHD and ischemic stroke: The Atherosclerosis Risk in Communities (ARIC) study. Atherosclerosis. 2007 Apr 7.
[13] Fox ER, Alnabhan N, Penman AD, Butler KR, Taylor HA, Jr., Skelton TN, et al. Echocardiographic Left Ventricular Mass Index Predicts Incident Stroke in African Americans. Atherosclerosis Risk in Communities (ARIC) Study. Stroke. 2007 Aug 30.
[14] Bikkina M, Levy D, Evans JC, Larson MG, Benjamin EJ, Wolf PA, et al. Left ventricular mass and risk of stroke in an elderly cohort. The Framingham Heart Study. Jama. 1994 Jul 6;272(1):33-6.
[15] Knutsen R, Knutsen SF, Curb JD, Reed DM, Kautz JA, Yano K. Predictive value of resting electrocardiograms for 12-year incidence of stroke in the Honolulu Heart Program. Stroke; a journal of cerebral circulation. 1988 May;19(5):555-9.
[16] Bikkina M, Larson MG, Levy D. Asymptomatic ventricular arrhythmias and mortality risk in subjects with left ventricular hypertrophy. J Am Coll Cardiol. 1993 Oct;22(4):1111-6.
[17] Auricchio A, Hartung W, Geller C, Klein H. Clinical relevance of stored electrograms for implantable cardioverter-defibrillator (ICD) troubleshooting and understanding of mechanisms for ventricular tachyarrhythmias. The American journal of cardiology. 1996 Sep 12;78(5A):33-41.
[18] Anderson KP. Sympathetic nervous system activity and ventricular tachyarrhythmias: recent advances. Ann Noninvasive Electrocardiol. 2003 Jan;8(1):75-89.
[19] Podrid PJ, Fuchs T, Candinas R. Role of the sympathetic nervous system in the genesis of ventricular arrhythmia. Circulation. 1990 Aug;82(2 Suppl):I103-13.