ARIC Manuscript Proposal #2076

PC Reviewed: 3/12/13  Status: A  Priority: 2
SC Reviewed: _________  Status: ___  Priority: ____

1.a. Full Title: Ventricular Premature Complexes (VPCs) and risk of dementia hospitalization: the ARIC study

b. Abbreviated Title (Length 26 characters): VPC and risk of dementia

2. Writing Group:
   Writing group members: Han Wang, Rebecca Gottesman, Alvaro Alonso, Thomas Mosley, Sunil Agarwal, Ross Simpson, Others Welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _HW_ [please confirm with your initials electronically or in writing]

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3. Timeline:
This proposal is going to be used for a Capstone Project (MPH) at Johns Hopkins Bloomberg School of Public Health. To achieve this aim, we plan to start statistical analysis immediately upon approval of the proposal and start drafting of the manuscript soon after. We expect to have completed at least the initial analysis by May 2013, with possible submission to a meeting soon after.

4. Rationale:
The prevalence of dementia in United States is growing over time (1), and is projected to continuously grow as health care improves and baby boomers age (3,4), which is likely to bring a high economic burden (2). Alzheimer’s disease (AD), the most common type of dementia in the United States, (5) is progressive, and current available treatments are mostly symptomatic (6). The progressive nature and lack of effective interventions emphasize the importance of a preventive approach. Previous studies (7, 8, 9) have shown that cardiovascular risk factors, such as hypertension, diabetes mellitus, and hypercholesterolemia, are closely related to development of mild cognitive impairment (MCI) and AD (10). Heart failure and atrial fibrillation are also identified as risk factors of AD (11, 13).

Ventricular premature contractions/complexes (VPCs) are frequently found in the general population, and are often considered as a benign arrhythmia (26). Antiarrhythmic medications or radiofrequency ablation may be provided for symptomatic patients (14, 15). Studies have shown that having a high burden of VPCs is associated with sudden cardiac death (27), reduced left ventricular systolic function and heart failure (16, 19). In addition, VPCs have been associated with incident stroke in the ARIC study (18). Stroke is not only associated with vascular cognitive impairment (CVI) (34), but also Alzheimer’s disease (33). With the evidence of the association between stroke and dementia, we suggest a hypothesis that VPCs may be associated to AD by serving as a vascular marker, in addition to cholesterol, diabetes and hypertension. We propose to evaluate if 1) VPCs are associated with dementia, and 2) if this association may be independent of stroke.

5. Main Hypothesis/Study Questions:
We propose to evaluate the association between ventricular premature contractions/complexes (VPCs) and the risk of dementia hospitalization in the ARIC study. We hypothesize that:
   1. Isolated ventricular premature contractions/complexes (at baseline) will be associated with higher hazard of dementia hospitalization in the ARIC study.
   2. The association will be stronger for people with higher burden of ventricular premature contractions/complexes, with a dose-response type of relationship.
   3. The association will be independent of stroke (we plan to exclude individuals with stroke in a secondary analysis).

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).

Study population
Participants in the ARIC study who had both a baseline EKG performed and cognitive tests at visit 2 will be included (therefore all included participants need to have come to visit 2). We will exclude individuals with low performance (below sex- and age-specific 5th percentile) on cognitive tests at visit 2 (28). For the primary analysis we will allow individuals with incident stroke up to the point when they develop stroke, and for the secondary analysis will include individuals with stroke at any point (or prevalent stroke at baseline).
Participants with missing information or prevalent history of stroke will be excluded. Participants with missing values for the 12-lead electrocardiogram or 3-lead 2-minute rhythm strip or those with cardiac rhythm disturbances such as Wolf-Parkinson-White syndrome, atrial fibrillation/flutter, wandering atrial pacemaker, supraventricular tachycardia, or non-sinus rhythm will be excluded.

**Exposures**

A standard supine 12-lead electrocardiogram at rest and a 2-minute 3-lead (leads II, V1, and V5) rhythm strip were recorded during baseline examination. The primary exposure will be the presence of any VPC on the 2-minute rhythm electrocardiogram. VPCs seen on a 2-minute ECG rhythm strip are highly correlated with high-frequency VPCs seen on 24-hour recordings\(^{(17)}\). VPCs were classified by the frequency of their occurrence on the 2-minute rhythm strip (i.e., single VPC, two to three VPCs, four or more VPCs)\(^{(24)}\).

**Outcome ascertainment**

The primary outcome of interest for this analysis was incident dementia identified through ARIC follow-up for all hospitalizations through 2010 (anticipated) and chart abstraction of all hospital discharge codes. Hospitalizations in ARIC are identified by participant or proxy report in the annual follow-up and by surveillance of local hospital discharge lists. The ICD-9 codes used to define dementia referred to Alzheimer's disease (331.0), vascular dementia (290.4) or any other code that could have been used for dementia of other etiology (290.0, 290.1, 290.2, 290.3, 290.9, 294.1, 294.2, 294.8, 294.9, 331.1, 331.2, 331.8, 331.9). ARIC participants with low scores (below sex- and age-specific 5\(^{\text{th}}\) percentile) in any of the cognitive tests at visit 2 will be excluded, so we will assume these cases to be incident events, as was done in the previously published paper\(^{(28)}\).

Incident stroke was identified through annual telephone interviews, triennial field center examinations, hospital discharges, death certificates, physician questionnaires, coroner/medical examiner reports, and informant interviews\(^{(28)}\).

**Statistical analysis**

We will study the association between VPCs at baseline and the risk of dementia hospitalization using Cox proportional hazards models. The main outcome variable will be time elapsed since visit 2 to dementia hospitalization, death or last known follow-up, whichever occurs first. VPCs will be evaluated as the primary exposure of interest: first as a binary variable (present/ absent), and also as a categorical variable including the number of VPCs, in different models. We will run a first model including age, sex, and race as independent variables. Then, we will run a second model adding systolic blood pressure, use of antihypertensive medications, diabetes, BMI, hypercholesterolemia and smoking at baseline, field-center and education. Finally, we will add apoE genotypes to examine a proven association and whether it confounds the other risk factors. As a secondary analysis, we will include individuals with prevalent stroke at baseline or
incident stroke during the follow-up period, so we can evaluate if this relationship is present in stroke patients (and compare the result to the primary analysis).

**Limitations**
The main limitation in this study is the method of outcome ascertainment. Dementia is not a disease usually requiring hospitalization, and thus we will possibly underestimate the incidence of dementia in our population. In the ARIC study, however, it has been shown that cognitive test performance is highly associated with increased hazard of dementia hospitalization, using the same methods to define dementia hospitalization.\[23\]

Second, we expect a high level of misclassification between different types of dementia. Therefore, our primary analysis will focus on dementia as a whole but not on Alzheimer’s disease or vascular dementia separately.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ___ Yes  ___ 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_DÑA = “CVD Research” would be used?  ___ Yes  ___ No
(This file ICTDER03 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  ___ 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  ___ 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)?


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/

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.

Reference


