ARIC Manuscript Proposal #1978

1.a. Full Title:
Covert vascular disease of the brain and risk of sudden cardiac arrest

b. Abbreviated Title (Length 26 characters):
Brain and sudden cardiac arrest

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

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3. **Timeline:**

Analyses will start and continue throughout the summer of 2012. A hiatus of nine months will be needed from October 2012-June 2013 due to Melody Hwang’s other academic commitments, but analyses will continue June 2013 and thereafter.

4. **Rationale:**

Vascular disease of the brain manifest as white matter hyperintensities and subclinical infarcts found on brain magnetic resonance imaging (MRI) is common in the elderly, is usually covert with the participants never having a stroke or transient ischemic attack, and is associated with cardiovascular risk factors and adverse health outcomes.\(^1,2\) The prevalence of covert vascular disease of the brain ranges from 10-20% in adults to 94% in the elderly, making it more common than overt disease of the brain.\(^2,3\) Neuropathologic studies have shown that these covert vascular findings may reflect arteriosclerosis and structural changes in the small vessels of the brain, such as in the arteries, arterioles, capillaries, and veins.\(^4-6\) More specifically, white matter hyperintensities have been found to correspond to demyelination, gliosis, axons loss, dilated perivascular spaces, spongiosis, and arteriosclerosis.\(^4-7\) The prevailing opinion is that white matter hyperintensities and infarcts share a common vascular, notably ischemic, pathophysiology.\(^1\)

The covert MRI-defined white matter hyperintensities and subclinical infarcts are strongly associated with age, hypertension, cognitive decline, carotid atherosclerosis, and stroke.\(^8,9,13,15\) White matter hyperintensities have also been found to be associated with sex, education, ethnicity, income, cigarette smoking, alcohol use, physical activity, homocysteine, diabetes mellitus, cholesterol, medication use (acetylsalicylic acid, clopidogrel, calcium blockers, ace inhibitors, antihypertensives, statins), myocardial infarction, heart failure, ankle arm index, dementia, mortality, claudication, brain infarcts, factor VIIc activity, fibrinogen, forced expiratory volume, gait disturbance, depression, and disability.\(^8,10-12\) Subclinical brain infarcts are additionally associated with sex, education, ethnicity, alcohol use, homocysteine, creatinine, medication use (aspirin), myocardial infarction, heart failure, ankle arm index, dementia, mortality, CABG, white matter changes, sleep apnea, atrial fibrillation, and transient ischemic attack.\(^9,13\)

The interconnections between the brain and the heart have long been recognized anecdotally and there is now substantial evidence that changes in the brain may affect cardiac electrophysiology and arrhythmia either through a mechanism of microvascular disease or autonomic nervous system dysfunction.\(^14\) Ultimately, the goal of this study is to identify novel risk factors for sudden cardiac arrest and to point to novel mechanisms that might contribute to these events. Given that sudden cardiac arrest is the leading cause of cardiovascular disease deaths in the United States, the findings of this study could have substantial public health impact by helping to identify ways to reduce the burden of sudden cardiac arrest in older community-dwelling adults.

5. **Main Hypothesis/Study Questions:**
Specific Aim 1: To test whether MRI-defined white matter hyperintensities of the brain are associated with an increased risk of sudden cardiac arrest.

MRI-defined white matter hyperintensities are scored on an ordinal scale from grade 0 (no white matter signal abnormalities) to grade 9 (all white matter involved). Sudden cardiac arrest is defined as a sudden pulseless condition occurring out of hospital or in the emergency room in an otherwise stable individual in the absence of a non-cardiac cause and will be categorized as “definite/probable” or “possible”. These sudden cardiac arrest categories may need to be combined if there are low numbers. We hypothesize that participants with high white matter grade will have an increased risk of sudden cardiac arrest compared to participants with low white matter grade. Additionally, we hypothesize that as white matter grade increases, the risk of sudden cardiac arrest will also increase.

Specific Aim 2: To test whether MRI-defined subclinical brain infarcts are associated with an increased risk of sudden cardiac arrest.

MRI-defined subclinical brain infarcts are characterized by number, location and size of infarcts (<3mm versus ≥3 mm). Sudden cardiac arrest is defined as described above. We hypothesize that participants with one or more MRI-defined subclinical brain infarcts will have an increased risk of sudden cardiac arrest compared to participants without MRI-defined subclinical brain infarcts. Additionally, we hypothesize that, as the number and size of MRI-defined subclinical brain infarcts increase, the risk of sudden cardiac arrest will also increase.

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).

Subjects for these analyses will include the 1,930 participants who underwent an initial brain MRI at two study sites (Forsyth County, North Carolina; Jackson, Mississippi) between 1993 and 1995. To include only people with covert vascular disease of the brain, participants will be excluded if they have had an overt event such as stroke or transient ischemic attack prior to their MRI. In ARIC, 1.5% participants had a stroke or transient ischemic attack before their first MRI scan, so these individuals will be excluded.

Variables of interest include sudden cardiac arrest, white matter grade, white matter location, white matter symmetry, brain infarct size, brain infarct number, and brain infarct location. Variables that will be considered as potential confounders since they are associated with both the exposure and outcome include demographic variables (age, sex, income), cardiovascular risk factors (cigarette smoking, alcohol use, physical activity, systolic blood pressure, fasting glucose, hypertension, diabetes, homocysteine, creatinine, ankle-arm index, forced expiratory volume, cholesterol), medication use (beta blockers, antihypertensives, diuretics, statins, ace inhibitors, calcium blockers, aspirin) and history of cardiovascular diseases (myocardial infarction, heart failure). Also, incident myocardial infarction and heart failure events during follow-up will be considered as potential mediators. EKG findings will be considered as either a confounder (marker or subclinical disease) or as a mediator.
We will provide descriptive statistics on participants in the analysis stratified by white matter disease grade and number and size of subclinical brain infarcts. Most of the previous studies examining white matter disease have quantified white matter hyperintensities continuously on a scale from grade 0 to 9 for analyses and have quantified MRI-defined subclinical brain infarcts continuously based on the number of infarcts.\textsuperscript{8,13} We will determine whether any of the white matter grades or number of brain infarcts should be further combined using the AIC statistic. For example, white matter grade could be collapsed into categories of 0-1, 2, 3, and 4 or more.

We will estimate the association between white matter grade and sudden cardiac arrest and the association between subclinical brain infarct and sudden cardiac arrest using Cox proportional hazards models, with significance defined at the alpha=0.05 level. The proportional hazards assumption will be tested using scaled Schoendfeld residuals and techniques such as stratification will be used for any variables that violate the assumption. Participants that do not have a sudden cardiac arrest will be censored when they die or are lost to follow-up. Multivariable analyses will be conducted using the rich longitudinal data on risk factors, subclinical disease, and clinical disease prior to the brain MR. Variables that will be considered as potential confounders since they are associated with both the exposure and outcome include demographic variables (age, sex, income), cardiovascular risk factors (cigarette smoking, alcohol use, physical activity, systolic blood pressure, fasting glucose, hypertension, diabetes, homocysteine, creatinine, ankle-arm index, forced expiratory volume, cholesterol), medication use (beta blockers, antihypertensives, diuretics, statins, ace inhibitors, calcium blockers, aspirin) and history of cardiovascular diseases (myocardial infarction, heart failure). Also, incident myocardial infarction and heart failure events during follow-up will be considered as potential mediators. EKG findings will be considered as either a confounder (marker or subclinical disease) or as a mediator. The following models will be used:

**Model for white matter hyperintensities and sudden cardiac arrest**

\[
\lambda(t|x) = \log\lambda_0(t) + \beta_1X_{\text{WHITE MATTER HYPERINTENSITIES (Yes/No)}} + \beta_2X_{\text{WHITE MATTER GRADE}} + \\
\beta_3X_{\text{DEMOGRAPHIC VARIABLES}} + \beta_4X_{\text{CVD RISK FACTORS}} + \beta_5X_{\text{MEDICATION USE}} + \beta_6X_{\text{CVD HISTORY}} + \beta_7X_{\text{EKG FINDINGS}}
\]

Where:
\[
\beta_2 = (\text{white matter grade } - 1) \text{ if grade}>0, \text{ or equals 0 if white matter grade}=0
\]

**Models for subclinical brain infarcts and sudden cardiac arrest**

\[
\lambda(t|x) = \log\lambda_0(t) + \beta_1X_{\text{SUBCLINICAL INFARCT (Yes/No)}} + \beta_2X_{\text{NUMBER OF INFARCTS}} + \beta_3X_{\text{DEMOGRAPHIC VARIABLES}} + \beta_4X_{\text{CVD RISK FACTORS}} + \beta_5X_{\text{MEDICATION USE}} + \beta_6X_{\text{CVD HISTORY}} + \beta_7X_{\text{EKG FINDINGS}}
\]

Where:
\[
\beta_2 = (\text{number of infarcts } - 1) \text{ if number of infarcts}>0, \text{ or equals 0 if number of infarcts}=0
\]

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 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  ___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)?

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.
References