ARIC Manuscript Proposal #2408

PC Reviewed: 8/12/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: ECG P-Wave Morphology and the Risk of Incident Ischemic Stroke

b. Abbreviated Title (Length 26 characters): **P-Wave Morphology and Stroke**

2. Writing Group:

Writing group members: Hooman Kamel, MD
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. [HK]

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3. Timeline:

Analysis to begin after Publication Committee approval. Manuscript anticipated for initial P&P review in Jan-Feb 2015.

4. Rationale:

One-third of ischemic strokes are classified as cryptogenic because a definite source cannot be found after standard evaluations (Marnane et al, 2010). Many cryptogenic strokes appear radiographically to have resulted from embolism (Hart et al, 2014). It has long been thought that a substantial proportion of these embolic-appearing cryptogenic strokes are due to undiagnosed paroxysmal atrial fibrillation/flutter (AF) (Kishore et al, 2014), but in a recent randomized trial of heart-rhythm monitoring after cryptogenic stroke, only 30% of patients had any evidence of AF after 3 years of continuous monitoring (Sanna et al, 2014), indicating that subclinical AF does not account for the majority of cryptogenic strokes. Instead, recent evidence suggests that some proportion of cryptogenic strokes may be associated with left atrial disease in the absence of AF. Supraventricular dysrhythmias such as frequent premature atrial contractions or paroxysmal supraventricular tachycardia have been associated with stroke even in the absence of clinically apparent AF (Binici et al, 2010; Kamel et al, 2013). We have recently found an association between P-wave terminal force in lead V_1 ($PTFV_1$), a widely used ECG marker of left atrial abnormality (Hancock et al, 2009), and stroke in the Multi-Ethnic Study of Atherosclerosis (Kamel et al, in press). The association between $PTFV_1$ and stroke did not substantially change whether we adjusted for incident AF or not, and remained the same in analyses that excluded patients with any incident AF during follow-up, suggesting that $PTFV_1$ may reflect an atrial cardiopathy that predisposes to stroke even in the absence of AF. If this hypothesis is true, atrial cardiopathy may explain some proportion of cryptogenic strokes, and may eventually prove to have implications for antithrombotic strategies for stroke prevention.

We have previously found an association between $PTFV_1$ and incident stroke in ARIC (Soliman et al, 2009), but this analysis did not compare different stroke subtypes. Our hypothesis about atrial cardiopathy and stroke risk would be further supported by demonstrating a stronger association between $PTFV_1$ and non-lacunar as opposed to lacunar stroke or hemorrhagic stroke, since this would suggest a specific link between $PTFV_1$ and cardiac embolism rather than general vascular risk. Therefore, we propose to examine the hypothesis that $PTFV_1$ is associated with incident ischemic stroke, and specifically that it is more strongly associated with non-lacunar rather than lacunar stroke or hemorrhagic stroke. The ARIC study provides a valuable opportunity to examine this hypothesis given the availability of baseline digital ECGs, large number of outcome events, and adjudication of stroke subtypes.

5. Main Hypothesis/Study Questions:

a) $PTFV_1$ is associated with incident ischemic stroke independent of AF
b) $PTFV_1$ is more strongly associated with incident non-lacunar stroke than with lacunar stroke or hemorrhagic stroke

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).

Design

Secondary data analysis collected prospectively from the ARIC cohort study.

Inclusion/Exclusion Criteria

We will include all participants with baseline ECG data. We will exclude participants with prevalent AF or prevalent stroke at baseline.

Outcomes

The primary outcome will be any incident ischemic stroke. Secondary outcomes will be incident non-lacunar ischemic stroke, incident lacunar ischemic stroke, and incident hemorrhagic stroke (ICH and SAH).

Variables

The predictor variable will be $PTFV_1$, defined as the duration (ms) multiplied by the amplitude (μV) of the downward deflection (terminal portion) of the P-wave in ECG lead V_1 (Soliman et al, 2009). $PTFV_1$ measurements will be obtained from the 12-lead ECG performed at the baseline visit.

A key covariate will be incident AF, which will be ascertained based on 12-lead ECGs at visits 2 through 4, hospital discharge records, and death certificates (Alonso et al, 2009). Other covariates will be ascertained from the baseline visit: age, sex, and race; low density lipoprotein cholesterol level; body mass index; cigarette smoking; and prevalent hypertension (defined as a blood pressure ≥140/90 mm Hg or current use of antihypertensive medication), coronary heart disease, congestive heart failure, and diabetes.

Statistical Analyses

Baseline covariates will be summarized and stratified by $PTFV_1$ dichotomized at 4,000 μV*ms, a level often used in clinical practice. Cox proportional hazards analysis will be used to examine the association between $PTFV_1$ and stroke. In analyses of specific stroke subtypes, participants will be censored at the time of any stroke (ischemic or hemorrhagic). Based on prior work, we will exclude $PTFV_1$ values >99.9th percentile as outliers, and model $PTFV_1$ as a continuous variable in 1-standard deviation increments; in our prior work, generalized additive models confirmed the linearity of associations between $PTFV_1$ and stroke despite the frequent occurrence of zero values for $PTFV_1$ (Kamel et al, in press). We will test the proportional hazards assumption by examining Schoenfeld residuals. Model 1 will adjust for demographic characteristics. Model 2 will include covariates from Model 1 plus the baseline covariates above. Model 3 will include covariates from Model 2 plus incident AF as a time-varying covariate. Since clinically apparent AF is often preceded by a long period of subclinical AF (Healey et al, 2012), a sensitivity analysis will model incident AF as a time-fixed covariate (i.e., we would assume that incident AF was present since baseline in a subclinical form). Bootstrapping will be

used to estimate the differences (and associated 95% confidence intervals) between the hazard ratios associated with $PTFV_1$ for different stroke subtypes. In secondary analyses, we will also evaluate $PTFV_1$ as a binary variable dichotomized at 4,000 μV*ms and at the 95th percentile. Based on prior work, we will examine interactions between $PTFV_1$ and age, sex, and race in relation to stroke risk (Soliman et al, 2009). Lastly, we will perform a secondary analysis in which $PTFV_1$ will be modeled as a time-varying covariate that takes the value of the measurement at the latest study visit.

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 ICTDER 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
ARIC Manuscript Proposal #1156- Soliman**:** Ethnic distribution of ECG predictors of atrial fibrillation and its impact on understanding the ethnic distribution of ischemic stroke in the Atherosclerosis Risk in Communities (ARIC) study.

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.

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