ARIC Manuscript Proposal #3960

PC Reviewed: 11/9/21 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Electrocardiographic deep terminal negative of the P wave in V1 and risk of ischemic stroke

b. Abbreviated Title (Length 26 characters): DTNPV1 and stroke

2. Writing Group:

Writing group members: Mingfang Li, Yuekai Ji, Youmei Shen, Wendy Wang, Elsayed Z. Soliman, Minglong Chen, Lin Yee Chen, others welcome.

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

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3. Timeline: Statistical Analysis: 1 month
Manuscript Preparation: 2 months

4. Rationale:

Arial fibrillation (AF) is independently associated with stroke, accounting for one in five ischemic strokes[1,2]. However, findings from recent studies have suggested that AF might not be the principal driver for left atrial thrombogenesis and cardioembolic stroke[3]. Atrial myopathy—manifesting as atrial fibrosis, electrical and autonomic remodeling, and a pro-thrombotic state in the atrium—elevates thromboembolic risk independent of AF[3]. P-wave indices on 12-lead ECGs are used to characterize atrial electrical activity. Abnormal P-wave indices, including advanced interatrial block[4], abnormal P-wave terminal force in V1 (PTFV1)[5], and abnormal P-wave axis[6], have been shown to be independently associated with ischemic stroke. Electrocardiographic deep terminal negative of the P wave in V1 (DTNPV1) is a simplified ECG metric of abnormal PTFV1, reflecting the underlying left atrial remodeling. However, the association of DTNPV1 with the risk of ischemic stroke is not well established. We hypothesize that DTNPV1—a routine and simple measure on 12-lead ECGs—would predict the risk of stroke in the general population secondary to cardiac thromboembolism.

5. Main Hypothesis/Study Questions:

AIM: Evaluate the association of DTNPV1 with ischemic stroke

Hypothesis: DTNPV1 will be significantly associated with an increased risk of ischemic stroke and cardioembolic stroke independent of AF and other stroke risk factors.

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: We will include all participants at the baseline visit (V1). We will exclude those with prevalent stroke, missing covariates, and missing ECG data or uninterpretable ECG due to AF.

Exposure

DTNPV1 will be defined as the absolute value of the depth of the terminal negative phase >100 μV in the presence of biphasic P wave in V1.

PTFV1 will be defined as the duration (ms) x the absolute value of the depth (μV) of the downward deflection (terminal portion) of the P-wave in lead V1. Abnormal PTFV1 is defined as ⩾4000 μV*ms similar to previous ARIC papers.

Outcome

Potential cases of stroke will be identified by annual phone interviews, and review of hospital discharge records and death certificates. Each case will be classified in accordance with criteria from the National Survey of Stroke by a computer algorithm and physician reviewer as previously described[7]. Discrepancies will be reviewed by a second physician. All definite thrombotic strokes will be classified as lacunar or nonlacunar stroke[8].

For our study, the primary outcome will be definite ischemic stroke, which includes all definite thrombotic stroke and all definite cardioembolic stroke. The secondary outcomes will include definite thrombotic stroke, definite cardioembolic stroke, definite thrombotic lacunar strokes and definite thrombotic nonlacunar stroke.

Statistical Analysis

Follow-up will be defined as time between the baseline exam until the date of ischemic stroke, death, or end of follow-up (through 2019). We will use Cox proportional hazards models with DTNPV1 as a time-dependent exposure variable to estimate hazard ratios and 95% confidence intervals of DTNPV1 for incident ischemic stroke, thrombotic stroke, cardioembolic stroke, lacunar stroke, and nonlacunar stroke. In order to compare the results of DTNPV1 to the results of abnormal PTFV1, we will estimate the association of abnormal PTFV1 with every outcome using Cox proportional hazards models.

We will construct 5 models.

Model 0: An unadjusted model

Model 1: Adjusted for age, sex, race, study center

Model 2: Model 1 additionally adjusted for smoking, body mass index, systolic and diastolic blood pressure, diabetes, coronary heart disease, left ventricular hypertrophy, heart failure, use of aspirin, and use of anticoagulants

Model 3: Model 2 additionally adjusted for use of other medications, including antihypertensive medications, anti-diabetic medications, and statins.

Model 4: Model 3 additionally adjusted for time-dependent AF

For all the outcomes, we will also consider restricted cubic spline regression to evaluate the association with outcome across the continuum of the amplitude of the terminal negative phase in V1 and PTFV1.

7. a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __x__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes __x__ No
(The 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 current derived consent file ICTDER05 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/aricproposals/dtSearch.html

___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)?

#2689 -aPWA associated with AF and ischemic stroke - Lin Yee Chen
#2408 – ECG P wave morphology and Ischemic Stroke – Elsayed Soliman
#1156 - Ethnic distribution of ECG predictors of atrial fibrillation and its impact on understanding the ethnic distribution of ischemic stroke- Elsayed Z. Soliman

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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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

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2. Wolf PA, Dawber TR, Thomas HE Jr., Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology*. 1978;28:973–977.
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