ARIC Manuscript Proposal # 3344

PC Reviewed: 5/14/2019   Status: _____   Priority: 2
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: Association of atrial fibrillation with incidence of extracranial systemic embolism: The ARIC Study

b. Abbreviated Title (Length 26 characters): AF and extracranial systemic embolism

2. Writing Group:

Writing group members: Mengyuan Shi, Lin Yee Chen, Wobo Bekwelem, Faye L.Norby, Elsayed Z.Soliman, Aniqa B.Alam, Alvaro Alonso

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

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3. Timeline:

 Statistical Analysis: 2 months
Manuscript preparation: 2 months

4.   **Rationale**:

Atrial Fibrillation (AF) affects an estimated 33.5 million patients worldwide and is associated with increased mortality and morbidity [1]. Although the causes of AF are only partially understood, many risk factors have been established (e.g., advancing age, male sex, hypertension, heart failure, and obesity) [2]. Cardioembolic stroke is one of the most important complications of AF, leading to substantial disability and mortality in these patients. Oral anticoagulation has demonstrated consistent effectiveness in the prevention of cardioembolic stroke among AF patients. The same mechanisms that lead to elevated risk of ischemic stroke in AF are also likely to increase risk of extracranial systemic embolism. A pooled analysis of recent clinical trials of anticoagulation in AF showed that 1 in 9 thromboembolic events in AF patients were extracranial systemic embolic events [3]. However, in contrast to the extensive epidemiologic evidence of increased risk of ischemic stroke in those with AF, no prior studies have evaluated the association of incident AF with the risk of extracranial systemic embolism.

Therefore, the goal of this proposal is to evaluate the association of AF with incidence of extracranial systemic embolism by comparing rates of extracranial systemic embolism in ARIC participants who developed AF versus those without AF.

5.   **Main Hypothesis/Study Questions**:

Aim 1: Evaluate the association of incident AF with incidence of extracranial systemic embolism.

Hypothesis: We expect a higher incidence of extracranial systemic embolism in persons with AF compared to persons without AF, after adjusting for confounding factors.

Aim 2: Identify determinants of extracranial systemic embolism, including CHA2DS2-VASc score and its components, in persons with AF.

Hypothesis: Persons with AF and a higher CHA2DS2-VASc score will have an increased risk of extracranial systemic embolism.

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 Design: prospective cohort study

Inclusion/Exclusion criteria:
Aim 1:
- **Inclusion:** ARIC participants without AF at baseline (visit 1)

- **Exclusion:** missing ECG at baseline, race other than white or black, non-whites from the Minnesota and Washington country centers, prevalent AF, missing covariates

Aim 2:
- **Inclusion:** ARIC participants with incident AF during follow-up
- **Exclusion:** missing AF status, race other than white or black, non-whites from the Minnesota and Washington country centers, missing covariates

Dependent Variable: Incidence of extracranial systemic embolism through the end of 2017. Incident extracranial systemic embolism will be defined based on presence of the following codes in any position as a discharge code in a hospitalization:
- ICD-9-CM 444.xx: Arterial embolism and thrombosis
- ICD10-CM I74.x: Arterial embolism and thrombosis

Positive predictive value of I74 has been reported to be 83%.[4]

AF ascertainment: As previously described, using study ECGs, hospital discharge diagnosis, and death certificates.[5]

Covariates: Sex, age, education, race-center, height, body mass index (BMI), smoking status, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, history of myocardial infarction, heart failure, stroke, and regular use of warfarin and anticoagulants.

Statistical analysis

Aim 1
We will use Cox proportional hazards models with AF status as a time-dependent variable to determine the association with incident extracranial systemic embolism, adjusting for baseline and time-dependent covariates.

We will explore effect measure modification by age, sex and race.

Aim 2
In patients with incident AF, we will first use variables from that time or the visit prior to AF to calculate the score at the time of AF, and then calculate the incidence rate of extracranial systemic embolism by score categories (0 to 9). We will run Cox proportional hazards models to compare levels of CHA2DS2-VASc score to a reference score of 0-1, after adjusting for covariates (age, sex, race/center, use of anticoagulants) at the time of AF diagnosis.

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_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 __×__ 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/mantrack/maintain/search/dtSearch.html

___×___ 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)?

No related manuscripts

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes ___×___ 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 https://www2.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.

Reference

[1] S.S Chugh, R. Havmoeller, K. Narayanan, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation, 129(8) (2014), pp. 837-847

[2] E.J. Benjamin, D. Levy, S.M. Vaziri, et al. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. JAMA, 271 (11) (1994), pp. 840-844

[3] Bekwelem W, Connolly SJ, Halperin JL, et al. Extracranial Systemic Embolic Events in Patients With Nonvalvular Atrial Fibrillation: Incidence, Risk Factor, and Outcomes. Circulation. 2015 Sep 1;132(9):796-803.

[4] Prat M, Derumeaux H, Sailler L, Lapeyre-Mestre M, Moulis G. Positive predictive values of peripheral arterial and venous thrombosis codes in French hospital database. Fundam Clin Pharmacol. 2018 Feb;32(1):108-113.

[5] Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Community (ARIC) study. Am Heart J.2009 Jul;158(1):111-7.