1.a. Full Title:

Temporal Trends in the Association of Incident Atrial Fibrillation with Stroke, Heart Failure and Mortality in the Atherosclerosis Risk in Communities Cohort

b. Abbreviated Title (Length 26 characters): Trends in Stroke and AF

2. Writing Group:

Writing group members: Zakaria Almuwaqqat, Lin Y. Chen, Elsayed Soliman, Alvaro Alonso, others welcome.

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:
September 2019 – Submit proposal
4. **Rationale:**

Atrial fibrillation (AF) is a major public health problem in the United States that is associated with significant morbidities and increasing risk of adverse cardiovascular events. [1] There is evidence that the prevalence of AF in the US is expected to increase more than 2-folds during the next 50 years. [2] Despite that rising AF incidence is partly related to enhanced surveillance, a dramatic and persistent excess risk of mortality was observed after AF diagnosis, underscoring the need for better control of AF-related outcomes.[3, 4] Acute ischemic stroke is one of the most devastating AF-related outcomes.[5, 6] Longitudinal data from the Framingham health study have shown consistent decline in stroke incidence after AF.[3] However there is recent indications that these trends may have leveled off. Overall, the age-adjusted stroke incidence has been rising with a disproportionate higher rate among US African American adults.[7, 8] A recent study in Olmstead county, MN community have shown that the risk of stroke after AF has ceased from declining over the past decade. However, this study was limited by the racial composition and dated back to 2010.[9] Similar findings have been reported for mortality and heart failure.[4, 10] Whether changes in the management of AF over time, including the approval of direct oral anticoagulants and the extended use of catheter ablation as a rhythm control strategy, have had an impact on outcomes in AF patients remains unclear.
5. **Main Study Questions:**

1) **Aim 1:** Estimate the temporal trends of incident stroke, heart failure and overall mortality in ARIC participants who develop AF.

2) **Aim 2:** Investigate the temporal trends in the association of AF with incident ischemic stroke, heart failure and mortality over time. We also will examine the trends by sex and race.

We hypothesize that the risk of stroke, heart failure and mortality associated to AF decreased early in the study period but this decrease has stabilized in the recent decade. We also hypothesize that the rate of decline could be disproportionate among different race and sex groups.

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 participants**

Eligible participants will be from the ARIC cohort with baseline examination data and follow up data on incident AF and stroke, heart failure and mortality.

**Exclusion criteria**

- Participants with prevalent stroke or prevalent heart failure.
• Participants with race other than white or black, as well as non-whites from the Minnesota and Washington County field sites (because of very small numbers).

Main exposure

Incident AF and year of diagnosis (continuous variable)- independent and joint association.

Outcome definition

• Incident stroke (definite and probable cases per adjudication)
• Incident heart failure
• All-cause mortality

Other Variables of Interest

Sex, age, race/center, education, height, systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking status, alcohol using status, diabetes, use of antihypertensive medications, LVH by ECG, incident HF, Anticoagulation use, CHAD VASc2 score and incident myocardial infarction (MI).

Analysis plan

For Aim 1, we will estimate age-specific rates of stroke, heart failure and mortality in participants with AF by decade (1987-97, 1998-2007, and 2008-2017). We will examine trends in rates of these outcomes using Poisson regression incidence rate ratios (IRRs) with calendar year/decade as the primary independent variable and adjusting for age, sex and race/center.

For Aim 2, we will examine the association of incident AF with incident stroke, HF and mortality
using AF as a time-dependent variable in a Cox regression model. We will assess interactions between calendar year at time of AF diagnosis and AF to determine whether the association of AF with endpoints has changed over time. We will adjust for age, sex, race/center and CHA2DS2-VASc score.

7.a. Will the data be used for non-CVD analysis in this manuscript? 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? 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

No overlap with existing proposals

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)?


- Temporal trends in validated ischaemic stroke hospitalizations in the USA. Int J of Epidemiology 2019 PMID 30879069

- No Decline in the Risk of Stroke Following Incident Atrial Fibrillation Since 2000 in the Community: A Concerning Trend. PMID: 27412902
11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes

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)* __2008.10 and 2009.16)

*ancillary studies are listed by number at http://www.cscu.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.cscu.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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript: No

References:
