1.a. Full Title: Atrial Fibrillation is Associated with Hospitalization for Dementia: The ARIC Study

b. Abbreviated Title (Length 26 characters): Atrial Fibrillation and Dementia

2. Writing Group:
   Writing group members: Lin Y. Chen, Alvaro Alonso, Faye Lopez, Thomas Mosley, Rebecca Gottesman, Rachel Huxley, Sunil K Agarwal, Laura R. Loehr, and others.

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

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3. Timeline:

Statistical Analysis: 3 months
Manuscript preparation: 3 months
4. **Rationale:**

Atrial fibrillation (AF) is the most common sustained arrhythmia afflicting more than 2 million Americans, a figure that is projected to increase to approximately 5 to 12 million by 2050.\(^1,2\) AF is not only associated with an increased risk of stroke,\(^3\) heart failure,\(^4\) and death,\(^5\) but it also imposes considerable socioeconomic burden.\(^6,7\)

Recently, there has been evidence to suggest that AF may contribute to the development of dementia—also a burgeoning public health problem. Notably, a cross-sectional study of the Rotterdam Study demonstrated that cognitive dysfunction was approximately twice as common in subjects with AF than in those without.\(^8\) Other cross-sectional studies have shown that AF was associated with cognitive dysfunction, independent of stroke and other cardiovascular risk factors.\(^9,10\) In contrast, analyses from some prospective cohort studies have not shown an association between AF and cognitive dysfunction.\(^11-13\) The Cognition in Atrial Fibrillation Evaluation (CAFE)\(^11\)—a prospective, longitudinal, community-based cohort study—did not find any association between AF and cognitive impairment. Similarly, two other prospective cohort studies did not find an association between AF and cognitive impairment in octogenarians.\(^12,13\)

More recent data from the Intermountain Heart Collaborative Study, an integrated health system database, have rekindled the debate on the association between AF and cognitive function.\(^14\) This study, which included 37,025 patients (10,161 with AF and 1,535 with dementia), not only demonstrated that AF independently predicted all dementia subtypes, but also showed that AF was a predictor of higher mortality among patients with dementia.\(^14\)

ARIC—with more than 1,000 incident AF events, data on hospitalized dementia, and mortality data—is uniquely suited to investigate the relationship between AF and hospitalized dementia, and the impact of AF on mortality in subjects with dementia.

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

**Aim #1: Evaluate the association of AF with hospitalization for dementia**

**Hypothesis #1**: ARIC participants who develop AF are more likely to be hospitalized for dementia than those who do not develop AF, independently of other risk factors for dementia.

**Aim #2: Determine the impact of AF on mortality in subjects who had been hospitalized for dementia**

**Hypothesis #2**: In subjects who had been hospitalized for dementia, the presence of AF increases mortality compared to those without AF.

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 study the entire ARIC cohort.
Exclusions: Missing information on study covariates and indeterminate AF status.

**Exposure measurement**

AF cases will be identified from:
1) Hospital discharge records (ICD-9 code 427.31 – Atrial fibrillation)
2) ECGs performed during study visits 1 – 4
3) Death certificates

**Outcomes measurement**

**Hospitalized dementia**

Hospitalizations for dementia will be identified by participant or proxy report in the annual follow-up and by surveillance of local hospital discharge lists. The ICD-9 codes that will be used to define dementia refer to Alzheimer disease (331.0), vascular dementia (290.4) or any other code that could have been used for dementia of other etiology [290.0 (senile dementia), 290.1 (presenile dementia), 290.2 (senile dementia with delusional features), 290.3 (senile dementia with delirium or confusion), 294.1 (dementia in conditions classified elsewhere), 331.1 (dementia in Pick’s disease), 331.2 (senile degeneration of brain), 331.8 (dementia with Lewy bodies), 331.9 (cerebral degeneration, unspecified)], as has been used in other ARIC publications.15

**Mortality**

Mortality is determined by cohort surveillance of the National Death Index as well as annual follow-up calls (with a surviving family member answering by proxy). We include death from all causes.

**Covariates**

Age, gender, race, study center, educational level, occupation, current smoking, body mass index, hypertension, diabetes, stroke, history of coronary heart disease or myocardial infarction, and heart failure.

Given that stroke is a probable intermediary in the causal pathway between AF and dementia, we will repeat the analyses with and without adjustment for stroke in the models. This will enable us to determine whether the association between AF and dementia, if any, is independent of stroke.

**Statistical analysis**

**Hypothesis #1**

We will use Cox proportional hazards models with AF status as a time-dependent variable to determine whether AF occurrence is associated with hospitalization for dementia, adjusting for covariates.

**Hypothesis #2**

We will estimate the post-hospitalization survival of participants hospitalized for dementia by the Kaplan-Meier method. We will determine the effect of AF status on survival of these subjects using Cox proportional hazards model, adjusting for covariates.
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

8.c. If yes, is the author aware that the participants with RES_DNA = ‘not for 
     profit’ restriction must be excluded if the data are used by a for profit group?  
     ____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.csec.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)?

    #1700: Cognitive function and incident dementia
    #1365: Cardiovascular risk factors and dementia hospitalization

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use 
      any ancillary study data?  ____x_ Yes  ____ No

11.b. If yes, is the proposal

     ___   A. primarily the result of an ancillary study (list number*___________) 
     ___x__ B. primarily based on ARIC data with ancillary data playing a minor 
      role (usually control variables; list number(s)* 1999.01 – ARIC MRI Study, 
      2008.12 AF ancillary study)
12. 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.

References
