ARIC Manuscript Proposal Form

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Publication Committee Review Date: **12/10/24**
ARIC Manuscript Proposal Number: **# 4581**

1.a. Full Title:
Atrial fibrillation burden and risk of heart failure and mortality in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters)AF burden and risk of HF

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group members:
Shengyuan Luo, Yunwen Xu, Sui Zhang, Mary Rooney, Amelia Wallace, Anum Minhas, Hau-Tieng Wu, Lin Yee Chen, Liz Selvin, Jung-Im Shin, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _SL____ **[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 (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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3. Timeline:
We aim to complete the manuscript within 1 year from the time of approval.

4. Rationale:

Atrial fibrillation (AF) is the most common type of sustained heart rhythm disorder. The global burden of AF is around 60 million and projected to rise. AF contributes to significant disease burden through elevating risks of stroke and heart failure (HF).[1] HF is a common pathway connecting various cardiovascular diseases to poor clinical outcomes and frequently co-exists with AF. Our understanding of the associations between AF and the development and progression of HF originates from historic observational studies that assessed AF as a binary entity based on diagnoses made with a 12-lead electrocardiogram during a clinical encounter.

However, AF is not a dichotomous disease trait – the proportion of time an individual spends in AF, i.e., AF burden, can be highly variable. On the one hand, short, asymptomatic AF known as subclinical AF is often clinically underdiagnosed. On the other, paroxysmal AF may progress to persistent AF which heralds worse health outcomes, and early AF ablations may lead to lower risk of HF presumably by reducing AF burden. To evaluate the prognostic significance of AF burden, recent observational studies leveraged medical claims data from patients with cardiac implanted electronic devices and demonstrated relationships between greater AF burden with not only more frequent HF hospitalizations but increased mortality.[2-4] Although cardiac implanted electronic devices allow for continuous heart rhythm monitoring whereby AF burden can be quantified, they are available only in select patient populations with existing conduction system abnormality and/or structural heart disease, limiting generalizability of research findings. Little high-quality epidemiology data exists to characterize AF burden and long-term HF and mortality risks in broader, ambulatory populations.

Technological advancements in continuous heart rhythm monitoring have enhanced our ability to manage AF in ambulatory settings. For example, the leadless ZioPatch (iRhythm) provides a means to the continuous ambulatory assessment of AF burden in those without implanted devices. In the ARIC Study, 1833 participants free of prevalent HF underwent 14-day iRhythm Zio XT Patch assessment for AF burden at visit 6 (2016-2017).[5] These participants also underwent active surveillance for HF in the ARIC Study up till 2021. These make the ARIC Study an ideal platform for a study to describe the link between AF and HF in the community-based population. We therefore propose this prospective cohort study on the associations between AF burden and the long-term risks of HF and mortality.

5. Main Hypothesis/Study Aims:

Our hypotheses are as follows:

1) Higher AF burden quantified by the Zio XT Patch during a continuous 14-day period will be independently associated with risk of incident HF;
2) Higher AF burden quantified by the Zio XT Patch during a continuous 14-day period will be independently associated with long-term mortality risk;

Our aims are the following

Aim 1: Examine the association between AF burden and risk of incident HF in those without prevalent HF.

Aim 2: Compare associations between AF, HF, and mortality among those with vs without a pre-existing clinical diagnosis of AF.

6. Design and analysis - please address the following aspects:

a) inclusion/exclusion

All participants with available 14-day Zio XT Patch and without prevalent HF at visit 6 will be included except for those missing AF burden data.

b) study design

Prospective study of visit 6 participants, examining the association of AF burden with the incidence of HF and all-cause mortality.

c) outcome and other variables of interest with specific reference to the time of their collection

Outcomes of interest include incidence of HF and all-cause mortality since visit 6 (2016-2017). Covariables at or prior to visit 6 include: age, sex, race, alcohol use, body mass index, smoking status, estimated glomerular filtration rate, history of diabetes, history of hypertension (based on systolic blood pressure and use of anti-hypertensives), coronary artery disease, and N-terminal pro-B-type natriuretic peptide.

d) summary of data analysis

We will use descriptive statistics to summarize participant characteristics at visit 6. We will use multivariable Fine-Gray models to assess the association between AF burden and HF risk accounting for the competing risk of mortality. We will use Cox proportional hazards regression to assess the association between AF burden with mortality risk. All analyses will be adjusted for age, sex, race, alcohol use, body mass index, smoking status estimated glomerular filtration rate, history of diabetes, hypertension, and coronary artery disease. A sensitivity analysis will additionally adjust for N-terminal pro-B-type natriuretic peptide.

e) Any anticipated methodologic limitations or challenges if present

Residual confounding due to the observational nature of the study.

f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ Yes ☒ 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** ☐ **No**
(The file ICTDER is distributed to ARIC PIs annually, 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 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 or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

☒ 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)?
Prevalence and characteristics of subclinical atrial fibrillation in a community-dwelling elderly population[5]

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☒ **Yes** ☐ **No → Skip to question 12**

11.b. If yes to 11.a., is the proposal

☒ **A. primarily the result of an ancillary study**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number #2014.18 (Chen)

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website□Ancillary Studies□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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website Publications Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

References:

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5. Rooney MR, Soliman EZ, Lutsey PL, Norby FL, Loehr LR, Mosley TH, Zhang M, Gottesman RF, Coresh J, Folsom AR, et al. Prevalence and Characteristics of Subclinical Atrial Fibrillation in a Community-Dwelling Elderly Population: The ARIC Study. *Circ Arrhythm Electrophysiol*. 2019;12:e007390. doi: 10.1161/circep.119.007390