ARIC Manuscript Proposal #3520

PC Reviewed: 12/10/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of Heart failure subtypes with incidence of newly-diagnosed atrial fibrillation: Data from the Atherosclerosis Risk in Communities Study.

b. Abbreviated Title (Length 26 characters): **Heart failure subtypes and atrial fibrillation.**

2. Writing Group:

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

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3. Timeline: September 2019 to March 2020

4. Rationale:

Atrial fibrillation (AF) and heart failure (HF) are major public health problems, having emerged as growing epidemics in developed countries, the US included (1) . It is estimated that by 2030, there will be over 12 million Americans with AF and 8 million with HF (2)(3). AF is a cause and also a consequence of HF. There exist differences among HF subtypes in atrial remodeling and outcomes associated with AF (4). Similarly, clinical outcomes after AF are somewhat influenced by HF subtypes (5). Almost two thirds of people with AF develop HF and

one third of people with HF develop AF (6). The frequent coexistence of AF and HF subtypes is strongly associated with an increase in morbidity and mortality (7).

Previous studies have explored the association between AF and HF. Most of these studies, however, are in hospital settings which limits the understanding of the sequence of occurrence of both conditions in relation to the other (8). A study done in a large community cohort – the Framingham Heart Study – was comprised mostly of Caucasian participants (6), limiting its generalizability to other racial groups. Also, the Framingham analysis could not differentiate the association between different HF subtypes and incident AF due to limited sample size. We seek to investigate the association of HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction (HFmEF) and HF with preserved ejection fraction (HFpEF) with the incidence and prevalence of AF in a large community-based racially diverse cohort wherein the temporality of AF and HF can be more accurately obtained.

5. Main Hypothesis/Study Questions:

Hypothesis

We hypothesize that risk of incident AF differs by HF subtypes. In addition, the prevalence of AF differs by HF subtypes.

Objectives

Primary

1. To assess the incidence of newly-diagnosed AF by HF subtype (HFrEF, HFmEF, HFpEF, no HF)
2. To assess the prevalence of AF by HF subtype (HFrEF, HFmEF, HFpEF, no HF)

Secondary

3. To assess sex and racial differences in the relationship between incident AF and HF subtypes.

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).

Inclusion/exclusion criteria

We will include all participants who attended the visit 5 (baseline for this analysis). Participants who have AF at this visit will be excluded from the incidence AF analysis. Participants whose AF status was not established at visit 1 will be excluded from the prevalent AF analysis. We will also exclude non-white or non-black participants, as well as non-whites from the Minnesota and Washington county sites.

Exposure

Main exposure is prevalent HF at visit 5. HF is defined as a prior hospitalization classified as definite, probable or chronic HF by adjudication (for hospitalizations after 2005 but before visit 5), a physician-reported diagnosis of HF, or hospitalization with an ICD-9-CM code 428.x in first position prior to 2005. HF subtypes will be determined based on left ventricular ejection fraction (LVEF) obtained by echocardiogram at visit 5. HEpEF is defined by LVEF $\geq$ 50%,

HFmEF is LVEF 40% - 49%and HFrEF is LVEF < 40%. Participants with prevalent HF as per prior definition but no information on LVEF will be categorized as 'unclassified' HF.

Outcome

The outcome for the incident AF analysis (objective 1) is defined as new onset AF after visit 5 (2011 to 2013) and up to 2017. The outcome for prevalent AF analysis is defined as AF between visit 1 to 5.

Diagnosis of AF is done using 1 of 3 sources: evidence of AF on a standard supine 12-lead resting ECG, hospitalization with an ICD-9-CM code 427.31 or 427.32 discharge code and if underlying cause of death was AF (ICD-10 code I48 or ICD-9 code 427.3)

Covariates

Based on previous studies, factors considered to be confounders include age, sex, race, study site, body mass index, systolic and diastolic blood pressure, smoking history, use of antihypertensive medication, diabetes mellitus, other cardiovascular diseases (myocardial infarction) and estimated glomerular filtration rate.(6,9)

Data analysis

The baseline prevalence of AF among patients with prevalent HF subtypes at visit 5 will be calculated, stratified by age and sex. We would compare these proportions between White/Caucasian and Black/African American participants using Chi-squared tests. Multivariable logistic regressions will be used to examine the association between HF subtypes and prevalent AF adjusting for risk factors of AF.

The cumulative incidence of AF will be estimated using methods that consider death as a competing risk. A separate curve will be used for those with and without HF, and by type of HF for incident AF. Standardized incidence rates (sex and age adjusted) will be calculated. Multivariable Cox proportional hazards regressions will be used to examine the association between HF subtypes and incident AF adjusting for risk factors of AF.

Covariates will be taken from visit 5. HF subtypes will be classified as no HF, HFrEF, HFmEF HFpEF and unclassified HF.

We will conduct stratified analysis by sex and race to explore differences in the association between HF subtype and AF risk across these demographic groups.

Preliminary numbers

Because of concerns about limited sample size for some HF categories, we have examined the number of prevalent and incident AF cases among visit 5 participants (see tables below). As shown in the tables, numbers are adequate for HFpEF category but are more limited for other categories (HFrEF, HFmEF). We will take into account this limitation in the interpretation of our findings, potentially combining exposure categories if needed (e.g. HFrEF and HFmEF).

Prevalent AF analysis

N = 6,538

	No AF	Prevalent AF
No HF	5586	554
Unclassified HF	44	41
HFpEF (>=50%)	133	103
HFmEF (40-49%)	21	21
HFrEF (<40%)	16	19
Total	5800	738

Incident AF analysis

N = 5,800

	No AF	Incident AF
No HF	5033	553
Unclassified HF	35	9
HFpEF (>=50%)	96	37
HFmEF (40-49%)	12	9
HFrEF (<40%)	10	6
Total	5186	614

Racial subgroups

N=6520

	Black	White
No HF	1416	4706
Unclassified HF	42	43
HFpEF (>=50%)	69	167
HFmEF (40-49%)	6	36
HFrEF (<40%)	10	25
Total	1543	4977

Methodologic limitations

Participants who have HFrEF are most often severely ill and are more likely to miss visit 5. This may lead to selection bias. We will do multiple imputation or weighting to correct for this potential bias. Other limitations include method of AF ascertainment, which can lead to under ascertainment of subclinical and paroxysmal AF, and the definition of HF subtype, based on a single echocardiographic assessment.

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 ___X_ 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:

___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)? No

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 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.

References

1. Chugh Sumeet S., Havmoeller Rasmus, Narayanan Kumar, Singh David, Rienstra Michiel, Benjamin Emelia J., et al. Worldwide Epidemiology of Atrial Fibrillation. Circulation. 2014 Feb 25;129(8):837–47.

2. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of Current and Future Incidence and Prevalence of Atrial Fibrillation in the U.S. Adult Population. The American Journal of Cardiology. 2013 Oct 15;112(8):1142–7.

3. Mozaffarian Dariush, Benjamin Emelia J., Go Alan S., Arnett Donna K., Blaha Michael J., Cushman Mary, et al. Executive Summary: Heart Disease and Stroke Statistics—2016 Update. Circulation. 2016 Jan 26;133(4):447–54.

4. Melenovsky V, Hwang S-J, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ Heart Fail. 2015 Mar;8(2):295–303.

5. Sugumar H, Nanayakkara S, Prabhu S, Voskoboinik A, Kaye DM, Ling L-H, et al. Pathophysiology of Atrial Fibrillation and Heart Failure: Dangerous Interactions. Cardiol Clin. 2019 May;37(2):131–8.

6. Santhanakrishnan Rajalakshmi, Wang Na, Larson Martin G., Magnani Jared W., McManus David D., Lubitz Steven A., et al. Atrial Fibrillation Begets Heart Failure and Vice Versa. Circulation. 2016 Feb 2;133(5):484–92.

7. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. Eur J Heart Fail. 2009 Jul;11(7):676–83.

8. Cheng M, Lu X, Huang J, Zhang J, Zhang S, Gu D. The prognostic significance of atrial fibrillation in heart failure with a preserved and reduced left ventricular function: insights from a meta-analysis. Eur J Heart Fail. 2014 Dec;16(12):1317–22.

9. Alonso Alvaro, Krijthe Bouwe P., Aspelund Thor, Stepas Katherine A., Pencina Michael J., Moser Carlee B., et al. Simple Risk Model Predicts Incidence of Atrial Fibrillation in a Racially and Geographically Diverse Population: the CHARGE-AF Consortium. Journal of the American Heart Association. 2(2):e000102.