ARIC Manuscript Proposal #4090

PC Reviewed: 8/9/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Hospitalized infections and incident heart failure in the atherosclerosis risk in communities study

b. Abbreviated Title (Length 26 characters): Infection and incident heart failure

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

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3. Timeline: Analyses to begin summer 2022, completed Fall 2022. First draft by the winter 2022-2023

4. Rationale:
HF affects >37.7 million individuals globally. In the US, HF prevalence has been projected to increase by 46% between 2012 and 2030[1]. Patient prognosis after their first HF hospital admission is poor, with a <50% survival rate at five years[2]. Despite recent therapeutic advances in treating HF with reduced ejection fraction[3], HF remains a major problem and there are currently no effective therapies available for treating heart failure with preserved ejection fraction. A recent American Heart Association (AHA) Presidential Advisory emphasizes that the current pipeline for

development of novel therapies is flat and innovative solutions are urgently needed to counteract trends towards increasing rates of cardiovascular death[4,5].

Advancing knowledge about upstream causes of HF will be important for informing prevention efforts and reducing the burden of HF in the population. Infections are a potential risk factor for incident heart failure. However, few studies have evaluated infection as a risk factor of new onset HF[6,7] and HF subtypes. Prior studies have assessed infection and incident cardiovascular events[8-11]. Specifically, a study in ARIC evaluated in- and out-patient infection and risk of CHD and ischemic stroke showing that risk of CHD and ischemic stroke were higher after both in- and out-patient infection[10,12]. Additionally, infection has been established as a common primary cause of hospitalization in people with heart failure[13,14], supporting the notion that infections can influence cardiovascular parameters[15].

Limited data exist examining the relationship between infection and incident HF, HFrEF and HFpEF in large population-based settings. Additionally, there are no data investigating whether infection is differentially associated with HFrEF vs. HFpEF. Here we propose to examine, in ARIC, the relationship between infection and the following outcomes longitudinally: i) any HF and ii) HFpEF and HFrEF (starting in 2005).

5. Main Hypothesis/Study Questions:

Aim 1: Investigate if hospitalized infections are predictive of incident HF.
Hypothesis: Hospitalized infection will be associated with increased risk for incident HF.

Aim 2: Investigate if infections (inpatient) are differentially associated with incident HFrEF vs. HFpEF.
Hypothesis: Hospitalized infection will be associated with increased risk for both incident HFrEF and HFpEF.

Design and analysis

Study design
Prospective cohort study, utilizing data from (1) baseline (v1) to look at incidence of any HF event through the most recent follow-up (v7); and (2) starting in 2005 to look at incident HFpEF and HFrEF events through the most recent follow-up (v7).

Inclusion criteria
African American or white participants with non-missing demographic information and HF adjudication.

Primary Exposures
The primary exposure variable will be any hospitalized infection, based on ICD codes from surveillance of hospitalization discharge lists or abstracted from participant/proxy annual report. In an effort to capture major infection events, we will account only for infections in the first five positions of the ICD code listing. Both ICD-9 and ICD-10 codes will be included; we cross-walked ICD-10 to ICD-9 codes and reviewed for face validity. As the primary exposure,

hospitalization with infection, will be treated as a binary time-varying exposure (0 = *no hospitalization with infection*; 1 = *hospitalization with infection*).

In sub analyses, exposures will be further defined as infections due to each of the following infection types: I) Pneumonia; II) Urinary Tract Infection; III) Bloodstream Infection; IV) Cellulitis/Osteomyelitis. Additional infection subtypes will be considered based on clinical interest and having a sufficient number of infection events observed prior to HF onset.

Covariates & Potential Effect Modifiers
We will consider adjustments for the following variables: age, sex, education, race, center, insurance status, income, cigarette smoking, physical activity, body mass index, systolic blood pressure, blood pressure medication use, diabetes, HDL cholesterol, LDL cholesterol, lipid lowering medications, prevalent CHD, prevalent stroke, chronic kidney disease.

Outcomes
The primary outcome will be incidence of any HF and (starting in 2005) HFpEF and HFrEF. Time to outcome will be defined as the time from baseline until first diagnosis of HF, HFpEF or HFrEF censoring at death, the last available follow-up, or study withdrawal. The nature of person-time contributed (ie. exposed vs unexposed person-time) will be determined accounting infections as a time-varying exposure, as described above. We will also identify and remove instances where HF and infection were in the same hospitalization.

Statistical analysis
Participant characteristics will be described according to infection exposure status.

Longitudinal Analyses:
The primary analysis will be time-to-event using Cox proportional hazards model to assess if infection is predictive of incident HF, HFrEF or HFpEF. All participants free of any HF at baseline (v1) or 2005 for HFrEF and HFpEF will be considered. At the first occurrence of infection, the participant will start to contribute exposed person-time until first diagnosis of HF, death, last available follow-up, or study withdrawal. Starting in 2005 we will assess HFpEF and HFrEF as the primary outcome of interest. We will also identify and remove instances where HF and infection are in the same hospitalization and exclude events that occurred in the first 1 year to account for reverse causation.

Decisions about modeling will take place during the analysis. Preliminarily, we envision our models to be structured as follows:

- Crude model
- Model 1 will adjust for age, gender, race/center, education, and health insurance (sociodemographic variables)
- Model 2 will additionally adjust for cigarette status (never, former current), Physical activity (lifestyle)
- Model 3 will further adjust for BMI LDL, anti-hypertension medication, previous CHD, previous stroke, diabetes and SBP

Sensitivity analyses:
To assess infection as trigger of HF vs. an etiological contributor in a longer time horizon, a case-crossover design over a 30-day period will be used to investigate if hospitalized infections are predictive of incident HF and HF subtypes. We will also identify and remove instances where HF and infection are in the same hospitalization and exclude events that occurred in the first 1 year to account for reverse causation.

To assess concomitant occurrence of HF and infection we will assess what excluding HF events that occurred within ≦30 days, 30-90 days, 90 days-1 year, 1-5 years and 5-10 years looks like. We will also account for interim occurrence of other CVD subtypes (i.e., CHD, MI, stoke), and recurrent infections during follow-up

The results from these sensitivity analyses will inform if further restrictions should be incorporated into our analyses outline above.

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

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

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)?
ARIC Manuscript Proposal #2287
ARIC Manuscript Proposal #1197
ARIC Manuscript Proposal #2663
ARIC Manuscript Proposal #2894

ARIC Manuscript Proposal # 3139
ARIC Manuscript Proposal #3888
ARIC Manuscript Proposal #2871

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

_X__ A. primarily the result of an ancillary study:
The relevant study number is 2012.04.

___ 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 http://www.cscc.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.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.

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 ____ Yes __X__ No.

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