ARIC Manuscript Proposal # 3321

PC Reviewed: 1/8/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Coronary heart disease and risk of incident heart failure with preserved ejection fraction: the ARIC study (Atherosclerosis Risk in Communities)

b. Abbreviated Title (Length 26 characters): CHD and risk of incident HFpEF

2. Writing Group:

Writing group members: Jenine John, Amil Shah, Brian Claggett, Hicham Skali, Scott Solomon, Kunihiro Matsushita, Aaron Folsom, Suma Konety, Dalane Kitzman, Thomas Mosley, Patricia Chang, OTHERS WELCOME

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _JJ__ **[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: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 3 months.

4. Rationale:

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of heart failure cases, yet it is not as well-understood as heart failure with reduced ejection fraction (HFrEF) (1). Slightly more than half of HFrEF patients have a concomitant diagnosis of coronary heart disease (CHD), and CHD has been more strongly associated with HFrEF than with HFpEF (2, 3). Because of this, HFrEF is often considered a consequence of coronary artery disease, while HFpEF is often considered a result of advanced hypertension, obesity, metabolic disorders, and microvascular disease (4-8) However, although CHD prevalence is higher in HFrEF compared to HFpEF, its prevalence is considerably higher in HFpEF compared to persons free of heart failure (HF). This was highlighted by an autopsy evaluation that found significant CHD in 65% of HFpEF patients compared to only 13% of age-matched controls (7). Coronary angiography is infrequently utilized in the evaluation of acute heart failure (9), and CHD may therefore be underdiagnosed in HFpEF patients. Indeed, a recent study systematically performed coronary angiography in acute decompensated HFpEF patients and found that 79% of the 75 HFpEF patients had either significant coronary artery stenosis on angiography or a history of CHD (10).

CHD is an established – and powerful – risk factor for incident HF generally. Additionally, autopsy studies suggest that acute coronary events account for an appreciable proportion of deaths in patients with HFrEF, including those attributed to a nonischemic etiology (9). Coronary ischemia causes both systolic dysfunction and diastolic dysfunction (11, 12), and it is now established that both HFrEF and HFpEF are characterized by a combination of systolic dysfunction (manifest as abnormal ejection fraction or abnormal longitudinal strain) and diastolic dysfunction (3, 13, 14). CHD may therefore be an important contributor to the development of HFpEF. In fact, the extent of CHD in post-myocardial patients correlates with the risk of subsequent HFpEF (15). Interestingly, previous studies have suggested that the presence of CHD is a stronger predictor of HFpEF for women than for men, implying sex differences in the effects of CHD that may contribute to the higher prevalence of HFpEF in women (16, 17). The presence of CHD has been clearly associated with higher mortality in HFpEF patients (18-20), and observational data suggest that this increased mortality risk may be averted by coronary revascularization (19, 20). Despite the difference in outcomes, prior small studies of patients with prevalent HFpEF have not observed prominent differences in echocardiographic measures between those with versus without prevalent CHD (10, 20). They also did not observe prominent differences in troponin, a biomarker that is of interest in the study of HFpEF since troponin is associated with diastolic dysfunction in the setting of coronary microvascular disease (21).

Despite compelling existing data regarding the high prevalence of CHD in HFpEF, there is limited community-based data regarding the prognostic importance of CHD for the development of HFpEF. Furthermore, among persons with CHD with a preserved left ventricular ejection fraction (LVEF), there is limited data regarding the alterations in cardiac structure and function that may predispose to HF development.

5. Main Hypothesis/Study Questions:

Detailed clinical phenotyping and longitudinal event ascertainment make ARIC uniquely well-suited to address the prognostic importance of CHD in the development of HFpEF and to assess the CHD-associated alterations in cardiac structure and function that predispose to HFpEF development. In this study, we will: (1) determine the prognostic relevance of incident coronary heart disease (CHD) for subsequent HFpEF and HFrEF, and the prognostic relevance of incident HFpEF and HFrEF for subsequent CHD using longitudinal data on incident cardiovascular disease (CVD); (2) determine the echocardiographic and biomarker (i.e. troponin) correlates of prevalent CHD among participants with preserved LVEF using data from Visit 5; and (3) explore the extent to which CHD-associated echocardiographic measures account for the relationship between CHD and incident HFpEF using post-Visit 5 outcome data.

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).

Analysis 1: Impact of CHD on subsequent incident HF, HFpEF, and HFrEF

Analysis 1 will use January 1st, 2005, when adjudication for HF hospitalizations began, as baseline and will include participants who are free of HF at that time. Cox proportional hazard modeling will be employed to analyze the association of CHD with the outcome of subsequent incident HF and HF phenotype, modeling CHD as a time-varying covariate. When assessing incident HFpEF as the primary outcome, participants experiencing incident HFrEF and incident HF with unknown EF will be censored at the time of that event. Conversely, when assessing incident HFrEF as the primary outcome, participants experiencing incident HFpEF and incident HF with unknown EF will be censored at the time of that event. Additional sensitivity analyses will be performed in which all participants with incident HF with unknown EF will be considered either HFpEF or HFrEF cases. The models will be adjusted for additional clinical covariates (specified below), which will be obtained from Visit 4 and AFU surveys and will be assessed as time-varying covariates when appropriate.

Finally, we will assess the risk of incident CHD after a HF diagnosis by repeating the analysis with incident HF as a time-varying covariate, and with incident CHD as the outcome. This analysis will then be repeated for HFpEF and HFrEF separately.

Inclusion criteria: Participants in the study as of January 1st, 2005
Exclusion criteria:
    Prevalent HF as of January 1st, 2005
Assessment of incident HF after CHD
    Primary predictor: Prevalent or incident CHD
    Primary outcome: Incident HF/HFpEF/HFrEF
Assessment of incident CHD after HF
    Primary predictor: Incident HF/HFpEF/HFrEF
    Primary outcome: Incident CHD
Covariates: age, sex, race, center, BMI, HTN, DM, ever smoker, GFR, a fib, and other variables found to differ based on the primary predictor

Analysis 2: Impact of prevalent CHD as of Visit 5 on echo parameters and troponin at Visit 5 among HF-free participants with LVEF of at least 50%.
We will perform a cross-sectional analysis at Visit 5 of HF-free participants with LVEF ≥50%. Linear regression will be used to assess the association of prevalent CHD as of Visit 5 with echocardiographic parameters (listed below) and troponin at Visit 5.
Inclusion criteria: Participants who underwent echocardiography at Visit 5
Exclusion criteria: Prevalent HF at Visit 5, EF <50% on Visit 5 echocardiogram
Primary predictor: Prevalent CHD at Visit 5
Primary outcomes:

- Ejection fraction
- LV end-diastolic dimension
- Left ventricular mass index
- Septal thickness
- Posterior wall thickness
- Left atrial volume
- Septal e'
- Septal E/e'
- Average peak longitudinal strain
- Hs-Troponin

Covariates: age, sex, race, center, BMI, HTN, DM, ever smoker, creatinine, a fib, and other variables found to differ based on primary predictor

Analysis 3: Extent to which CHD-associated echocardiographic and biomarker measures account for the relationship between CHD and incident HF, HFpEF, and HFrEF

Cox proportional hazards modeling will be employed to assess the association of prevalent CHD at Visit 5 with the outcome of subsequent incident HF and HF phenotype, and analyses will be performed to assess the extent to which troponin and the echocardiographic parameters that are significant in Analysis 2 account for these associations. Participants with MI after Visit 5 will be censored at that time.
When assessing incident HFpEF as the primary outcome, participants experiencing incident HFrEF and incident HF with unknown EF will be censored at that time. We will perform analyses assessing HFrEF, incident HF with unknown EF, death, and post-visit 5 MI as competing risks. When assessing incident HFrEF as the primary outcome, participants experiencing incident HFpEF and incident HF with unknown EF will be censored at that time. We will perform analyses assessing HFpEF, incident HF with unknown EF, death, and post-visit 5 MI as competing risks. Additional sensitivity analyses will be performed in which all participants with incident HF with unknown EF will be considered either HFpEF or HFrEF cases. The models will be adjusted for additional clinical covariates (specified below) obtained from Visit 5.

Inclusion criteria: Participants who underwent echocardiography at Visit 5
Exclusion criteria: Prevalent HF at Visit 5
Primary predictor: Prevalent CHD at Visit 5

Primary outcome: Incident HF/HFpEF/HFrEF
Covariates: echocardiographic parameters that are found to be significant in Analysis 2, age, sex, race, center, BMI, HTN, DM, ever smoker, creatinine, a fib, and other variables found to differ based on primary predictor

Additional analyses will be performed with stratification by sex and by race.

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

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

__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)?

#3072, "Temporal Trends in Heart Failure Following Myocardial Infarction: The Atherosclerotic Risk in Communities Study" – Drs Shah and Clark on the writing group of this proposal.

#1835, "Subclinical Atherosclerosis, Glucose Status and Incident Heart Failure: The Atherosclerosis Risk in Communities Study"- published; assessed carotid intima-media thickness rather than CHD

#1551, “Characteristics, treatment and outcome in heart failure with preserved vs. reduced ejection fraction: The Atherosclerosis Risk in Communities (ARIC) Study”- proposes assessing comorbidities and predictors of mortality for HFpEF and HFrEF; does not propose assessing predictors for development of HFpEF/HFrEF (reviewed 9/2009)

#2536, “Predicting risk in heart failure with preserved ejection fraction- a model based on clinical features at hospital presentation”- published, Dr. Shah on the writing group of this proposal; assesses predictors of mortality rather than predictors for development of heart failure

#1709, “Racial and geographic comparisons in the presentation, co-morbid conditions and treatment in acute decompensated heart failure”- proposes to assess comorbidities of HF, does not assess predictors for development of HF (reviewed 10/2010)

#1376, “Optimal predictors of incident hospitalized heart failure: the ARIC cohort study”- published, assessed predictors for incident HF data up to 2007 (most of currently available adjudicated HF data not used)

#2155, “Patient Characteristics and Outcomes Associated with In-hospital Onset of Acute Decompensated Heart Failure (ADHF)”- published, specifically addressed ADHF that develops in-hospital

#1757, “The association of high sensitivity troponin with heart failure, mortality and recurrent coronary heart disease (CHD) in individuals with prevalent CHD”- proposes focusing on troponin, and does not divide HF into HFpEF and HFrEF (reviewed 3/2011)

#1891, “Phenotypic profile of heart failure with preserved ejection fraction in African Americans: risk factors, cardiac structure and function, and prognosis”- published, Dr. Shah on the writing group of this proposal; assessed comorbidities for HF and predictors of mortality, but did not address risk factors for development of HF

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 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.

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