ARIC Manuscript Proposal #3578

PC Reviewed: 3/10/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Temporal trends in signs and symptoms of heart failure and their prognosis among patients hospitalized with acute decompensation

b. Abbreviated Title (Length 26 characters): **Temporal trends in HF signs and symptoms**

2. Writing Group: Abhigna Kolupoti, Ambarish Pandey, Michael Hall, Muthiah Vaduganathan, Robert Mentz, Melissa Caughey

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _____ **[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: An abstract will be submitted to AHA Scientific Sessions 2020 within 3 months of proposal approval (abstract submission deadline = June 2020), and a manuscript will be completed within 1 year

4. Rationale:

Heart failure (HF) is a leading cause of morbidity and mortality globally. The overall prevalence of HF is about 1–2% worldwide with an estimated 64 million people affected, resulting in more than 1 million hospitalizations annually in both the United States and Europe. [1] In the United States alone, an estimated 5.7 million Americans ≥20 years of age have HF, based on data from NHANES 2009 to 2012.[2] The prevalence of HF is projected to increase 46% from 2012 to 2030, resulting in >8 million people ≥18 years of age with HF. [3]

HF can be categorized into subtypes with reduced ejection fraction (HFrEF) and heart preserved ejection fraction (HFpEF).[4] Although HFrEF was previously thought to be more common and has been more extensively studied, the incidence of HFpEF is increasing. The relative prevalence of HFpEF among all HF patients is approximately 50% and is increasing over time. An epidemiologic study from Olmstead County, Minnesota reported the prevalence of HFpEF relative to HFrEF to be increasing at a rate of 1% per year, indicating that HFpEF is an emerging epidemic and is on track to become the most common type of HF in the near future.[5] HFpEF is also associated with high mortality, and while survival in HFrEF has significantly improved over the past decades, prognosis of patients with HFpEF has not shown any significant change over the same time period.[5]

Although demographics, comorbidities, aetiology and pathology differ for patients with HFpEF and HFrEF[6], both groups present with similar clinical features of HF. While symptom-guided therapy is a conventional method of treatment, advanced imaging techniques, biochemical investigations and invasive hemodynamic assessments have shifted the focus away from the clinical examination. However, large-scale studies such as TIME-CHF have demonstrated non-inferiority of symptom-guided therapy to investigation guided therapies.[11] Further, many clinicians use symptom-based classifications such as the New York Heart Association (NYHA) HF classification to modulate treatment regimens; patients are often required to be persistently symptomatic despite initial medical therapies to be considered candidates for downstream interventions, including devices. Better understanding of the prognostic significance of clinical features and comorbidities in the treatment of patients with HFpEF and HFrEF may reduce the morbidity and mortality associated with HF, as well as improve the quality of life for millions of people globally.

Recent studies indicate that the cardiovascular physical examination has independent prognostic value, both for patients with HFrEF and HFpEF.[7,8] However, the role of comorbidities such as obesity and chronic lung disease, which are common with HFpEF, and their confounding effect on recognition of HF signs and symptoms may lead to misdiagnosis and inappropriate treatment due to either under- or over-appreciation of the risk of adverse outcomes.[9,10] Our recent work (ms#3369) suggests that obesity prevalence has increased with hospitalized ADHF during the 10-year period under surveillance, particularly among patients with HFpEF. We hypothesize that the overall prevalence and 10-year trajectories of HF signs and symptoms differ for patients with HFpEF vs. HFrEF. We will also explore whether temporal trends differ among obese vs. non-obese patients, women vs. men, and black vs. white patients. As a sensitivity analysis, we will examine whether temporal trends differ among patients classified with “definite” vs. “probable” acute decompensated heart failure. “Definite” classification requires evidence that a specific HF treatment (*e.g.*, diuresis) results in clinical improvement.[12] We will also examine associations between HF signs and symptoms and

mortality, examining both individual associations for each clinical feature and associations with burden (total number) of signs and symptoms.

5. Main Hypothesis/Study Questions:

1. What are the 10-year temporal trends (2005-2014) in HF signs and symptoms among patients who are hospitalized with ADHF?

-Does the annual prevalence of HF signs and symptoms change over time or remain stable?
-Do the aggregate (2005-2014) and annual prevalence differ for patients hospitalized with HFpEF vs. HFrEF?
-Do the aggregate (2005-2014) and annual prevalence differ for obese vs. non-obese patients?
-Do the aggregate (2005-2014) and annual prevalence differ by race or sex for patients hospitalized with ADHF?

2. What is the association between presence of HF signs and symptoms and mortality in patients hospitalized with ADHF?

-What is the association between individual HF signs and symptoms and mortality?
-What is the association between burden (total number) of HF signs and symptoms and mortality?
-Do the mortality associations differ over time, by HF type, by obesity, or by demographics?

Study Population

Patients hospitalized with heart failure, captured by the ARIC Heart Failure Community Surveillance (2005-2014).

Statistical Analysis

-All statistics will be weighted by the inverse of the sampling probability and will account for the stratified sampling design. Categorical variables will be compared using Rao-Scott χ^2 tests and continuous variables will be compared by the difference in least square means from weighted linear regression.
-Temporal trends in annual prevalence of HF signs and symptoms will be analyzed by logistic regression, by regressing year of admission as a continuous variable (analogous to the Cochrane-Armitage test for trend).
-Differences in annual prevalence trends will be analyzed by logistic regression, testing the multiplicative interaction of the comparator variable (race, sex, HF type, obesity status) with year of admission.
-Mortality associations will be analyzed using multivariable Cox regression, with minimal adjustment for age, race, sex, length of stay (a surrogate for hospitalization acuity), hospital, and year of admission. We will also construct a fully adjusted model additionally accounting for comorbidities.

Variables

We will consider temporal trends in HF signs and symptoms. These will include patient reported symptoms (*e.g.*, paroxysmal nocturnal dyspnea, orthopnea, hypoxia, edema, and shortness of breath), as well as physical exam findings (*e.g.*, jugular distension, hepatojugular reflux, rales,

ronchi, wheezes, and S3 heart sounds), and biomarkers / imaging signs (*e.g.*, BNP, left ventricular systolic function, diastolic dysfunction, pulmonary hypertension, right ventricular dysfunction, pulmonary edema, pleural effusion)

Limitations
-Data will be limited by availability in the medical record and abstraction priority
-Analyses of HFpEF and HFrEF will be limited by availability of in-hospital echocardiography results
-BNP laboratory values are not standardized across hospitals, and some hospitals used proBNP instead.
-Although relevant to this analysis, we will not have information on patient socioeconomic status

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).

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 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? ____ 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/mantrack/maintain/search/dtSearch.html

___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)?

MS#1607: Heart failure diagnostic schemes in hospitalized patients and follow up outcomes: The Atherosclerosis Risk in Communities (ARIC) Study [2010]

This investigation proposed to analyze the prognosis of various signs and symptoms (Aim #4) but is based on the cohort population rather than the community surveillance population and does not examine temporal trends. Although the proposal was submitted in 2010, the analysis Aim #4 results do not appear to be published

MS#2536: Predicting risk in heart failure with preserved ejection fraction – a model based on clinical features at hospital presentation [2015]

This investigation proposed to build a risk score for patients with HFpEF, based on clinical features (which would include signs and symptoms of HF). However, the published manuscript used the EFFECT risk score instead: doi: 10.1161/CIRCHEARTFAILURE.117.003992.

*We have contacted investigators from these previous proposals (Patricia Chang, Laura Loehr, Scott Solomon) but they declined collaboration on this proposal

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.

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