1.a. Full Title: Recurrent admissions for acute decompensated heart failure among patients with and without peripheral arterial disease: The Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): PAD and ADHF: ARIC Study

2. Writing Group: Zainali Chunawala, Patricia Chang, Andrew DeFilippis, Michael Hall, Kunihiro Matsushita, 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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3. Timeline: Abstract to be completed in time for AHA Scientific Sessions 2019 (deadline = June 6). Manuscript to be completed within 1 year of proposal approval
4. Rationale:

Peripheral arterial disease (PAD) is a common comorbidity in patients with heart failure. In a cross-sectional multicenter study of patients with heart failure with reduced ejection fraction (HFrEF), the overall prevalence of PAD (determined by ankle-brachial index) was reported to be 17.1%. When stratified by race and ethnicity, prevalence of PAD was 25.9% for white patients, 13.4% for Hispanic patients, and 13.7% for black patients (1). The prevalence of PAD likely differs for patients with HFrEF vs. heart failure with preserved ejection fraction (HFpEF), particularly if the etiology of HFrEF is ischemic cardiomyopathy secondary to coronary disease. Data from NHANES suggests the prevalence of PAD in individuals with coronary disease is 13% (2). Similarly, an association between PAD and coronary disease was reported in the Peripheral arterial disease detection, awareness, and treatment in primary care (PARTNERS) program, which examined prevalence of PAD in patients >70 years of age, or 50-69 years of age if smokers. PAD was detected in 1865 (29%). Overall, 13% of patients had PAD only, 16% had PAD and cardiovascular disease (CVD), 24% had CVD only (3).

In patients with heart failure, PAD has been associated with mortality and all-cause hospitalizations (4,5). However, no studies have examined the impact of PAD on recurrence of acute heart failure hospitalization. This is surprising, considering that PAD may be a contributing factor to heart failure (6-9). It is also uncertain whether outcomes of PAD in patients with acute decompensated heart failure (ADHF) differ by heart failure type, demographics, or comorbid conditions. We hypothesize that PAD is independently associated with recurrent acute heart failure admissions and death, and that its impact differs by heart failure type (HFrEF vs. HFpEF). We will also explore whether outcome of PAD differ by race, sex, or other comorbid conditions. To investigate this, we will examine heart failure surveillance data captured by the ARIC cohort study from 2005-2017.

5. Main Hypothesis/Study Questions:

1. What is the prevalence of diagnosed PAD among patients hospitalized with ADHF? Does the association differ by HFpEF vs. HFrEF? Does the association differ within demographic subgroups?

2. Is concomitant PAD associated with recurring ADHF admissions? Does the association differ by HFpEF vs. HFrEF? Does the association differ within demographic subgroups? Does the association differ by presence of other comorbid conditions?

3. Is concomitant PAD associated with death in patients hospitalized with ADHF? Does the association differ by HFpEF vs. HFrEF? Does the association differ within demographic subgroups? Does the association differ by presence of other comorbid conditions?
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).

Study Population:
ARIC cohort members hospitalized with definite or probable ADHF 2005–2017, with at least one year of follow up for subsequent ADHF readmissions or death.

Exposure:
Patients with or without concomitant peripheral vascular disease (HFAA11M). This variable was abstracted from the medical record and includes any mention of peripheral arterial disease, intermittent claudication, lower extremity arterial disease (LEAD), and history of peripheral arterial bypass surgery. Alternatively, discharge codes may be used to classify PAD in these patients as a sensitivity analysis. For hospitalizations after visit 5 (2011-2013), we will also consider a sensitivity analysis defining PAD by ABI measurements.

Outcomes:
Recurring admission for physician-adjudicated acute decompensated heart failure within 30-days and 1-year of the index hospitalization discharge date
Death within 30-days and 1-year of the index hospitalization discharge date

Analytical Plan

- Each recurring ADHF readmission per patient will be counted within 30 days and 1 year of the index hospitalization discharge date

- Crude incidence rates for ADHF readmissions, death, and composite will be calculated by summing all occurrences of the outcomes of interest, divided by the total amount of person-time at risk. Time at risk will be defined by the duration of time following discharge from the index hospitalization for ADHF, and will be truncated at either 30 days or 1 year

- Hazard ratios of acute heart failure readmissions, death, or composite will analyzed using repeat-events Cox regression, with robust estimators accounting for within-subject correlation between recurring readmissions. Models will be adjusted for demographics, year of admission, and comorbidities associated with peripheral arterial disease (such as diabetes, CKD, hypertension, coronary heart disease).

- Separate models will be constructed among subgroups based on heart failure type, demographic group, and concomitant comorbidities. Statistical interaction will be tested by the multiplicative interaction of PAD with variables of interest (heart failure type, race, sex, and concomitant comorbidities)

Limitations

- Data are limited to availability in the medical record and abstraction priority
-Diagnoses of peripheral vascular disease not verified or adjudicated by standardized ARIC physician review of the medical record.

-Classification of HFrEF and HFpEF limited to patients with available inpatient echocardiography or a historical ejection fraction abstracted within 2 years prior to the hospitalization.

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/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)?

   MP#3108: Predictors of recurrent CVD current events
   MP#1778: Predictors of 30-day readmission among heart failure patients
   MP#2852: Hospital readmissions for patients hospitalized with acute decompensated heart failure and preserved vs. reduced ejection fraction
   MP#2022: Peripheral arterial disease and risk of incident heart failure in the Atherosclerosis Risk in Communities Study

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://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.

References

   Arterial Disease in Patients With Heart Failure by Race and Ethnicity. Congestive Heart Failure.
   2010;16(3):118-121.

2. Selvin E, Erlinger T. Prevalence of and Risk Factors for Peripheral Arterial Disease in the

3. Hirsch A. Peripheral Arterial Disease Detection, Awareness, and Treatment in Primary Care.

   peripheral arterial disease on outcomes in advanced chronic systolic heart failure: a propensity-

5. Sandesara PB, Hammadah M, Samman-Tahhan A, Kelli HM, O'Neal WT. Peripheral artery
disease and risk of adverse outcomes in heart failure with preserved ejection fraction. Clin


