ARIC Manuscript Proposal # 3369

PC Reviewed: 3/12/19   **Status: _____**   **Priority: 2**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: Temporal trends in comorbidities among patients hospitalized with heart failure

  b. Abbreviated Title (Length 26 characters): **HF comorbidity trends**

2.   Writing Group:
    Writing group members: Ambarish Pandey, Muthiah Vaduganathan, Sameer Arora, Arman Qamar, Robert Mentz, Sanjiv Shah, Patricia Chang, Stuart Russell, Wayne Rosamond, 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 prepared for AHA Scientific Sessions 2019 (abstract deadline is in June 2019). Following this, a manuscript will be drafted. We anticipate completing the manuscript within 1 year of the manuscript proposal acceptance

4.   Rationale:

It has often been commented that acute decompensated heart failure (ADHF) hospitalizations have become increasingly more complex. Beyond mere antidote, contemporary analyses from the Get With the Guidelines registry and the Clinical Practice Research Datalink report an increasing prevalence of both cardiovascular and non-cardiovascular comorbidities among patients hospitalized with heart failure[1,2]. However, across the 2005-2014 study interval, acute heart failure hospitalizations became increasingly predominated by heart failure with preserved ejection fraction (HFpEF)[1,3]. Compared to heart failure with reduced ejection fraction (HFrEF), HFpEF is more often burdened by excessive comorbidities[4,5]. Thus, it is unclear whether the temporal comorbidity trends reflect increasing medical complexity of patients hospitalized with acute HF, or an increasing predominance of HFpEF.

Changing patient demographics may also explain the increasing prevalence of comorbidities during this study period. Relative to HFrEF, HFpEF is more often associated with elderly, white, women. However, despite the increasing predominance of HFpEF reported by the GWTG from 2005-2014, a decreasing proportion of patients hospitalized with acute HF were observed to be white (73% to 67%) or women (76% to 74%) across the study interval[1]. Comorbidity burden is likely to differ by race and sex among patients hospitalized with acute HF, and sex- and race-specific trends in comorbidity burden may change over time as well. Importantly, many comorbid conditions may be modifiable, presenting actionable areas for intervention.

However, it is uncertain whether increasing comorbidities are unique to hospitalized patients with acute heart failure, possibly triggering the acute decompensation. Alternatively, an increasing temporal pattern of comorbidities may also be observed in patients with stable, chronic heart failure who are hospitalized for other causes.

We propose to examine temporal trends in patients hospitalized with ADHF using community surveillance data captured by the ARIC study from 2005-2014. We will examine comorbidity prevalence changes over time, and whether rates of change in comorbidity prevalence differ for ADHF vs. chronic stable HF. We will also examine differences in rates of change of temporal comorbidity prevalence among subgroups of patients with ADHF, comparing HFpEF to HFrEF, black patients to white patients, and men to women. Additionally, we will examine annual temporal trends in length of stay (LOS) for patients with ADHF, as a measure of patient acuity.

5.   Main Hypothesis/Study Questions:

1. What are the 10-year temporal trends (2005-2014) in comorbidities among patients who are hospitalized with ADHF?
   -Does the annual prevalence of comorbidities change over time or remain stable for patients hospitalized with ADHF?
      -Does the prevalence and rate of change in comorbidity prevalence differ for patients hospitalized with ADHF vs. chronic, stable HF?
      -Does the prevalence and rate of change in comorbidity prevalence differ for patients by heart failure type (HFpEF vs. HFrEF) for patients hospitalized with ADHF?
      -Does the prevalence and rate of change in comorbidity prevalence differ by race or sex for patients hospitalized with ADHF?

2. What are the 10-year temporal trends (2005-2014) in average LOS among patients who are hospitalized with ADHF?
    -Does the annual average LOS change over time?
    -Does the annual average LOS differ for HFrEF vs. HFpEF?
    -Does the annual average LOS differ by race and sex?

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
Patients hospitalized with heart failure, captured by the ARIC Heart Failure Community Surveillance (2005-2014). Our study population will include ADHF patients and a comparison group of hospitalized patients with chronic, stable HF.

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 prevalence of comorbidities will be analyzed by logistic regression, by regressing year of admission as a continuous variable.
-Differences in rate of change of comorbidity prevalence will be analyzed by logistic regression, testing the multiplicative interaction of the comparator variable (race, sex, HF type) with year of admission.

Sensitivity Analyses
-Dichotomized comorbidities may not adequately capture disease management or severity. Consequently, we will conduct several sensitivity analyses. These will include analyses of obesity (BMI >35 kg/m^2), anemia (<10 g/dL), uncontrolled hypertension (SBP >140 mmHg) and stage 3a or higher CKD (eGFR <45 mL/min per 1.73 m^2)
-We will also examine temporal trends in hospitalization severity based on the GWTG-HF risk score.
-Because there is no consensus on ejection fraction used to define HFpEF vs. HFrEF, we will use an EF of 50%, and conduct a sensitivity analysis using a cutpoint of 40%.

Variables
We will consider temporal trends in both cardiovascular and non-cardiovascular variables. These may include obesity, hypertension, diabetes, anemia (from hospital hemoglobin labs), glomerular filtration rate (from hospital creatinine labs), smoking, sleep apnea, COPD, depression, thyroid disease, atrial fibrillation/flutter, peripheral vascular disease, and coronary artery disease

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
-Laboratory values may be influenced by hemodilution, particularly if measured at admission. For this reason, we will analyze the "last" laboratory value recorded in the abstractions.
-Most HF hospitalizations captured by the ARIC community surveillance were female patients. Consequently, sex-stratified analyses may have limited statistical power.
-We will not have information on medications / treatment for comorbid conditions (except for hypertension) because these were not collected by the ARIC surveillance.
-Although relevant to this analysis, we will not have information on patient socioeconomic status

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)?

MP#1569: The heart failure population burden due to acquired risk factors: The Atherosclerosis Risk in Communities study (2009).
Coauthors Rosamond and Chang are on this manuscript proposal.

MP#1709: Racial and geographic comparisons in the presentation, co-morbid conditions and treatment in acute decompensated heart failure (2010)
Coauthors Rosamond and Chang are on this manuscript proposal.

MP#2281: Race and Gender Differences in Heart Failure with Preserved Ejection

Fraction: Morbidity, Case Fatality, and their Determinants (2013)
Coauthors Chang and Russell are on this manuscript proposal.

MP#2600: The Association of Obesity with HF Phenotypes in the ARIC Study (2015)
Coauthor Russell is on this manuscript proposal.

MP#1490B: Utilization of Optimal Medical Therapy for Hospitalized HF and Outcomes (2009).
This is related to medication patterns by race and sex, and not comorbidity trends.
Coauthor Rosamond is on this manuscript proposal

MP#2434: Trends in Incidence and Mortality of ADHF (2012).
This was published in 2018 and does not address comorbidity trends
Coauthor Chang is on this manuscript proposal.

MP#2155: Patient Characteristics and Outcomes Associated with In-Hospital Onset of ADHF (2013).
This was not related to temporal trends, and the focus was in-patient onset ADHF
Coauthors Caughey, Rosamond, and Chang are on this manuscript 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.

References

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2. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV, Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet.* 2018; 391: 572-580.

3. Chang PP, Wruck LM, Shahar E, Rossi JS, Loehr LR, Russell SD, Agarwal SK, Konety SH, Rodriguez CJ, Rosamond WD. Trends in Hospitalizations and Survival of Acute Decompensated Heart Failure in Four US Communities (2005-2014): ARIC Study Community Surveillance. *Circulation.* 2018; 138: 12-24.

4. Mentz RJ, Kelly JP, von Lueder TG, Voors AA, Lam CS, Cowie MR, Kjeldsen K, Jankowska EA, Atar D, Butler J, Fiuzat M, Zannad F, Pitt B, O'Connor CM. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol.* 2014; 64: 2281-2293.

5. Kitzman DW, Shah SJ. The HFpEF Obesity Phenotype: The Elephant in the Room. *J Am Coll Cardiol.* 2016; 68: 200-203.