1.a. **Full Title**: Hospital readmissions for patients hospitalized with acute decompensated heart failure and preserved vs. reduced ejection fraction

b. **Abbreviated Title (Length 26 characters)**: Rehospitalization, HFpEF vs. HFrEF

2. **Writing Group**: Melissa Caughey, Patricia Chang, Sally Stearns, Carla Sueta, Amil Shah, Wayne Rosamond, *others welcome!*
   Writing group members:

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]

**First author:** Melissa Caughey  
Address: UNC Cardiology  
232 EPA Bldg.  
Chapel Hill, NC 27599

Phone: (919) 843-1841  
Fax / Email: caughey@med.unc.edu

**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).

Name: Patricia Chang  
Address: UNC Cardiology  
Chapel Hill, NC 27599

Phone: (919) 843-4069  
Fax: (919) 966-1743  
E-mail: patricia_chang@med.unc.edu

3. **Timeline**: 1 year after proposal approval
4. **Rationale:**

Each year, ~6 million Americans with heart failure spend a collective total of ~6.5 million days in the hospital\(^1\). Heart failure is not only a leading cause of hospitalization for Medicare beneficiaries, but also the most common discharge diagnosis for patients subsequently rehospitalized within 30 days\(^2\). In fact, nearly a third of the 750,000 patients over 65 discharged with heart failure each year\(^3\) are reported to be rehospitalized within 30 days; however, the majority of readmissions (63%) are for causes other than heart failure\(^2\).

Given the high costs associated with heart failure management, the Center for Medicare Services now requires mandatory reporting of 30-day all-cause readmissions for patients discharged with heart failure\(^4\). Accordingly, risk-adjusted readmission models have been developed to assess hospital performance, and are currently endorsed by the National Quality Forum. Risk models account for likelihood of readmission by adjusting for demographics and 35 comorbid conditions, including heart failure\(^5,6\). However, no effort is made to account for the competing risk of death\(^7\), or distinguish the cause of readmission. It is also questionable whether risk models adequately adjust for differences in heart failure patients with preserved or reduced ejection fraction. Patients with HFrEF are particularly prone to hospitalization for causes unrelated to heart failure, even when well-managed\(^7,8\). Finally, risk-adjusted readmission models utilized by NQF have also been criticized for poor discrimination (AUC=0.60), and short duration of follow up time\(^7\).

Previous analyses from heart failure registries have extended readmission outcomes beyond the mandatory 30 day reporting period, and have included patients with HFpEF and HFrEF\(^9-14\). However, the majority have analyzed all-cause readmission or death as a composite, secondary outcome. Although a Polish registry of 661 patients hospitalized with heart failure reported a trend for greater death/readmission after one year of follow up among patients with HFrEF vs. HFpEF (40% vs. 32%; p=0.07)\(^11\), the majority reported no difference in composite death / all-cause mortality over 6-months, 9-months, or 1-year. However, with the exception of an Italian registry of 1,669 heart failure patients, none examined heart failure as a specific cause of 1-year readmission\(^13\). Further, none considered repeat hospitalizations for the same patient, which is not an unlikely outcome for patients with heart failure.

The ARIC Cohort study is well suited to examine short and long-term readmissions for definite/probable acute decompensated heart failure among patients with HFpEF and HFrEF. Because cohort members were closely followed, repeat hospitalization analysis is also possible. In addition, the ARIC study includes CMS linked data for cohort members covered by Medicare, allowing a longitudinal analysis all-cause rehospitalizations.

5. **Main Hypothesis/Study Questions:**

1. Do 30-day, 6-month, 1-year, and 2-year rehospitalizations and mortality differ between cohort members with definite/probable hospitalized ADHF and preserved ejection fraction ≥50% (HFpEF) compared to those with ADHF with reduced ejection fraction (HFrEF)?
   a. Do these estimates differ when counting multiple rehospitalizations for ADHF and accounting for death, compared to counting only one composite outcome and censoring after the first event?
2. In the subset of ARIC Cohort Medicare beneficiaries, do 30-day, 6-month, 1-year, and 2-year \textit{all-cause} rehospitalizations and mortality differ among patients discharged with definite/probable hospitalized ADHF and preserved ejection fraction $\geq 50\%$ (HFpEF), compared to reduced ejection fraction (HFrEF)?
   a. Do these estimates differ when counting multiple rehospitalizations and accounting for death, compared to counting only one composite outcome and censoring after the first event?

3. Do outcomes differ when defining HFrEF and HFpEF by other EF cut-points (35\%, 45\%, 55\%), or by grouping heart failure into the 3 categories recommended by ESC and ACC/AHA HF guidelines ($<40\%$, 40-49\%, $\geq 50\%$ and $\leq 40\%$, 41-49\%, $\geq 50\%$, respectively)?

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 and Outcomes**

Our study population will consist of ARIC Cohort participants hospitalized from 2005 onward with definite or probable acute decompensated heart failure (ADHF). Patients will be followed for 30-day, 6-month, 1-year, and 2-year outcomes, using the first ADHF hospitalization with available EF data as the index visit. For the first aim, readmission outcomes will be limited to hospitalizations for ADHF confirmed by physician review of the medical record. In the subset of patients covered by Medicare, 30-day, 6-month, 1-year, and 2-year outcomes will be analyzed for all-cause rehospitalization and death.

**HFpEF and HFrEF Definitions**

Consistent with the majority of publications examining rehospitalization outcomes in heart failure patients\textsuperscript{9-14} and prior publications from ARIC\textsuperscript{15}, we will define HFpEF by an ejection fraction $\geq 50\%$, and HFrEF by an EF $< 50\%$. Ejection fractions will be based on available EF data abstracted from the hospital chart (although not necessarily from hospital visit echocardiograms). In a secondary analysis, heart failure type will be defined using ejection fractions from the subset of patients with in-hospital echocardiograms. Common historical EF cut-points for HFrEF/HFpEF will be evaluated (35\%, 45\%, 55\%), as well as groupings recommended by ESC and ACC/AHA HF guidelines ($<40\%$, 40-49\%, $\geq 50\%$ and $\leq 40\%$, 41-49\%, $\geq 50\%$, respectively)\textsuperscript{16, 17}.

**Statistical Analysis**

Hazard ratios of rehospitalization will be analyzed using multivariable Cox regression at specific time points and overall, for repeat measures and robust estimators to account for correlation between repeat events. Events will be censored at either death/30-days of follow up, death/6-months of follow up, death/1-year of follow up, or death/2-years of follow up. Outcomes will first be analyzed within sociodemographic strata, and statistical interaction will be assessed. Following this, multivariable models will be constructed, with possible adjustment for age, race, sex; as well as potential cofounders such as insurance status, index visit length of stay, and comorbid conditions.

**Limitations**

To avoid misclassification of readmission, we will not count transfers to other hospitals as rehospitalization. Additionally, our analysis will be limited to hospital patients with EF data. In
the ARIC surveillance of HF hospitalizations, EF data is not necessarily from echocardiograms performed during the hospital visit, which may be a potential limitation. To overcome possible misclassification of HFpEF/HFrEF, a sensitivity analysis of patients evaluated by in-hospital echocardiography will be carried out. The long-term rehospitalization outcomes may be limited by the possibility of recovered HFrEF, although the occurrence of this is low in the ARIC Cohort population (estimated ~3% in the community sample).

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)?

   MS#1951: Predictors of Medication Adherence After Hospitalization for Heart Failure in ARIC (PMCID: 4675666)
   MS#2650: Using Medicare Part D Phase to Identify Effects of Medication Adherence (PMID: 21430286)
   MS#1778: Predictors of 30-day readmission among heart failure patients (PMID: 21430286)

   Many of the authors of MS1951 and MS2650 are included on this proposal (Drs. Sueta, Stearns and Chang for MS1951 and MS2650; Dr. Chang for MS1778).

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/](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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](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 __x__ Yes __ __ No.

References


