1.a. **Full Title**: Predictors of Medication Adherence After Hospitalization for Heart Failure in ARIC

b. **Abbreviated Title (Length 26 characters)**: Drug Adherence in Heart Failure

2. **Writing Group**: Carla A. Sueta, Jo Ellen Rodgers, Anna Kucharska-Newton, Sally Stearns, Patty Chang, Mark Holmes, Hanyu Ni, Til Stürmer. Others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _CS_ [please confirm with your initials electronically or in writing]

**First author**: Carla A. Sueta  
**Address**: University of North Carolina  
UNC Center for Heart & Vascular Care  
160 Dental Circle  
CB #7075. 6th floor Burnett Womack Bldg, 6th floor  
Chapel Hill, NC 27599  
Phone: 919-843-5214  
Fax: 919-966-1743  
E-mail: carla_sueta@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**: Anna Kucharska-Newton  
**Address**: CVD Epidemiology Program  
Department of Epidemiology  
University of North Carolina at Chapel Hill  
137 E. Franklin St, Suite 306  
Chapel Hill, NC 27514  
Phone: 919-966-4564  
Fax: 919-966-9800  
E-mail: anna_newton@unc.edu

3. **Timeline**: 1 year after the receipt of part D data

4. **Rationale**: 

---

*ARIC Manuscript Proposal #1951*
Heart failure affects 6.6 million Americans and 23 million people worldwide and is increasing. There are more than a million hospitalizations per year in the US. Heart failure is one of the most common reasons for hospitalization in patients over the age of 65. Thirty-day readmission is also high, approaching 25% nationally. The Get With The Guidelines-Heart Failure (GWTG-HF) Registry reported that 10.3% of 54,322 heart failure hospitalizations during 2005-2007 were due to medication or dietary nonadherence. Although provider prescription rates for evidence-based therapies have improved over time and during hospitalization for heart failure, patient nonadherence is common and widely variable. Overall nonadherence to heart failure medications has been reported to be between 11 and 48%. Some studies have reported nonadherence rates for individual classes of medications- 11-65% for ACE-I/ARB, 19-43% for beta blockers, and 58-87% for aldosterone antagonists. Studies have reported both increasing and unchanged adherence over time. Data on medication adherence are not currently available in patients with heart failure with preserved ejection fraction.

Nonadherence is associated with poor outcomes. In Denmark, nonpersistence (break in therapy > 90 days) was linked to increased mortality in 107,092 patients discharged after first hospitalization with heart failure. In the US, nonadherence has been associated with increased all-cause mortality and cardiovascular hospitalizations. This association remained significant when all 3 classes of heart failure medications (ACE-I/ARB, BB, aldosterone antagonists) and when the components of the composite end point were considered separately. Increased readmissions, more Emergency Departments visits, subsequent higher length of stay, and higher health care cost have also been linked to nonadherence.

Several studies have investigated patient-related characteristics of medication adherence in heart failure patients but only a few have reported multivariable models. Generally, age > 65 years is associated with better adherence. However, in one study, patients < 65 years were more adherent to ACE-I/ARB and less adherent to BB compared to older patients. Decreased adherence has been associated with male gender in most studies. Dialysis, no insurance, African American ethnicity, history of heart failure, depression, new users of medications, failure to fill a prescription within 30 days of discharge, taking only one class of heart failure medications, and cost-related issues. Higher comorbidities or chronic illness score, high number of concomitant medications, and hospitalizations have been reported to be associated with both increased and decreased adherence. The study that reported a c-statistic for their multivariate model indicated that only a small proportion of the variability in medication adherence was explained by observed patient-related factors.

We will use data from the ARIC cohort study linked with the CMS Medicare claims data to examine adherence over time and predictors of medication adherence among study participants who have been hospitalized with heart failure. In contrast to previous studies of medication adherence, we will examine a more current cohort (2006-2009) of patients with an adjudicated hospitalization for heart failure. We will utilize Medicare part D claims as opposed to self-report or specific pharmacy data bases. ARIC coupled to CMS data will enable us to explore whether there is an association between medication adherence and patterns of hospital care and transitions of care and the outcomes of
nonadherent vs. adherent patients. If sample size is sufficient, predictors of medication adherence in patients with heart failure with preserved ejection fraction will be examined which has not previously been reported. Determining predictors of adherence in patients who have been hospitalized with heart failure will aid in designing interventions to improve medication compliance and outcomes.

5. Main Hypothesis/Study Questions:

1. Does medication adherence differ at 6 months compared to 1 year after hospitalization for heart failure?

2. Do patterns of care during hospitalization and at discharge influence medication adherence in the ARIC cohort who have been hospitalized with heart failure, i.e. cardiology consultation during hospitalization, ICU stay, length of stay, intravenous diuretics or inotropes, cardiac tests, cardiac procedures, newly started medications, follow up ≤ 2 weeks, collaborative care with a cardiologist, and referral to home health?

3. Does medication adherence differ by type of heart failure i.e. systolic vs. heart failure with preserved ejection fraction?

4. What are the outcomes of adherent compared to nonadherent patients?

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).

This is a retrospective, ARIC cohort analysis utilizing Medicare Part A (inpatient), B (outpatient), and D (pharmacy) claims data.

Inclusion/Exclusion Criteria:

1. Primary discharge diagnosis of both incident and prevalent heart failure hospitalizations between 2006 and 2009 validated by chart abstraction
2. Alive at discharge
3. Enrolled in Medicare Part A, B, and D.
4. Not directly discharged to a nursing home, skilled nursing facility or hospice

The beginning of follow up is defined as the date of hospital discharge for heart failure. The follow up period is 1 year. Adherence will be reported as semiannual and yearly medication possession ratio (MPR) based on Medicare part D data for eligible study participants. MPR is computed as the number of days supply obtained during the observation period divided by the number of days in the observation period multiplied by 100. MPR will be adjusted for subsequent hospital admissions by excluding the dates of those stays and calculated by censoring for death, lost to follow up, or at entry into a nursing home, skilled nursing facility, or hospice if that occurs after discharge.
Medication adherence is defined as MPR > 80%. Discontinuation is defined as a gap of > 30 days from the run out date of the previous prescription. We will continue to follow these patients to determine if the prescriptions are refilled at a later time. Persistence is defined as no discontinuations. The following classes of medications will be examined: ACE-I/ARB, BB, diuretics, digoxin, spironolactone, calcium channel blockers, and statins. We will also explore adherence to combinations of medications: ACE-I/ARB + BB, ACE-I/ARB + diuretic + BB, ACE-I/ARB + BB + diuretic + spironolactone.

Medication adherence will be reported as means and medians. Other data will be reported as means for continuous variables and as percentages for categorical variables. Univariate comparisons between adherent and nonadherent patients will be compared using the Pearson chi-square analysis for categorical variables and Student’s t test for continuous variables. Logistic regression will be used to identify predictors of medication adherence. The overall fit of the regression model will be assessed using a c-statistic. The analysis explanatory variables for medication adherence will focus on process of care variables including intravenous inotropes, ICU stay, length of stay, cardiology consultation, cardiac tests (echo, catheterization, nuclear study, cardiac MRI, cardiac CT, stress test), cardiac procedures (PCI, cardioversion, ICD, CRT), newly started medications, number of cardiac classes of medications at discharge, time from discharge to 1st medication refill, time to 1st follow up visit, follow up within 1 or 2 weeks of discharge, follow up with a cardiologist, and referral to home health. Patient characteristic variables will include: age, gender, and race, and ARIC study center, comorbidities including CAD, dialysis, lung disease, diabetes, ejection fraction or qualitative description of left ventricular function if known. Secondary analysis will examine adherence in systolic vs. diastolic heart failure if the sample size is sufficient.

We will compare the outcomes of adherent vs. nonadherent patients. Outcomes will include: death, hospitalization, admission to hospice, nursing home, or a skilled nursing facility derived from Medicare claims data. We recognize that outcomes will be affected by selection bias i.e. healthy adherers and frailty. We will explore several methods to address this issue i.e. adding frailty markers such as home oxygen, including a negative control outcome such as accidents, and consider utilizing a marginal structure model. We will also examine the best way to deal with the concurrence of exposure and outcome, and will consider survival models as well as other approaches.

This study has several limitations. A major limitation is that filling a prescription does not guarantee that the patient actually takes the medication. Furthermore, patterns of care such as follow-up visits are also chosen at least in part by the patient or the patient in conjunction with the physician rather than independently (randomly) assigned, so selection bias may affect the estimates. Sample size may also be modest because only a portion of patients will have Part D. There are also no specific measures of heart failure severity in ARIC which would correlate with healthcare resource utilization and outcomes. We will use ejection fraction (EF) as a surrogate defining EF ≥ 50% or normal EF as HF with preserved ejection fraction, EF 40-49 or mild systolic, EF 31-39 or moderate, and EF ≤ 30% or severe systolic heart failure.
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.cscu.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)?

# 1490 Utilization of optimal medical therapy for hospitalized heart failure and outcomes: the ARIC Study. Dr. Chang is a member of the writing group. Her proposal does not address medication adherence.

# 1799 Continuity of physician care and outcomes among patients with heart failure. The Atherosclerosis Risk in Communities (ARIC) Cohort Study
#1884 Does collaborative care between primary care physicians and cardiologists improve outcomes or heart failure? Anna Kucharska-Newton is a member of the writing group. Her proposal does not address medication adherence.

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.

Bibliography


2. Hospitalcompare.gov


