ARIC Manuscript Proposal # 1490B

1.a. Full Title: Utilization of Optimal Medical Therapy for Hospitalized Heart Failure and outcomes: The ARIC Study (2005-2014)

b. Abbreviated Title (Length 26 characters): Optimal Heart Failure Therapy

2. Writing Group:
Writing group members: Lena Mathews, Ning Ding, Lisa M. Wruck, Rachel Kloss Silverman, Laura R. Loehr, Matthew Loop, Jung-Im Shin, Naresh M. Punjabi, Alain G. Bertoni, Deidra Crews, Wayne D. Rosamond, Chiadi Ndumele, Kunihiro Matsushita, Patricia P. Chang (others welcome)

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

First author: Lena Mathews, MD, MHS
Address: Johns Hopkins University School of Medicine
600 North Wolfe Street
Blalock /Room 524D2
Baltimore, Maryland 21287
Phone: 917-270-8339 Fax:
E-mail: lmathew6@jhmi.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 P. Chang, MD, MHS, FACC
Address: Division of Cardiology, CB 7075
The University of North Carolina at Chapel Hill,
160 Dental Circle, 6th Floor Burnett-Womack Building
Phone: (919)-843-4069 Fax: (919)-966-1743
E-mail: patricia_chang@med.unc.edu

3. Timeline:
Once the data is obtained, data analysis and manuscript preparation will be done in the next 6 months.

4. Rationale:
Heart failure (HF) is a growing epidemic, with an incidence of approximately 10 per 1000 in the population age >65 years and estimated prevalence of 6.5 million in Americans ≥ 20 years old.(1) Although most cases of HF are managed in the outpatient setting, however
Hospitalizations with HF are a significant cause of morbidity, mortality, and costs, with over 1 million hospitalizations in 2014. (1) Guidelines for the care of patients with chronic heart failure have been in place since 1995, with the most recent ACC/AHA version in 2017. (6)

Although standard therapy is better understood for heart failure with reduced ejection fraction (HFrEF), what is considered standard therapy for heart failure with preserved ejection fraction (HFpEF) is less well understood. Despite these guidelines, heart failure is still undertreated. (3, 4) Medications are often not optimized, especially to target doses, and life-saving devices such as defibrillators are underutilized. However, published reports to date about optimal therapy have been based on hospital registries which have been based on patient “volunteers” (e.g., OPTIMIZE-HF and ADHERE registries) (2-4) or hospital “volunteers” (Get With the Guidelines-HF registry) rather than a population sample. Some of these registries (5) do not have follow-up data and all of these registries are biased by the fact that someone at that institution has enough of an interest in heart failure to participate.

The overall differences and temporal trends in the use of appropriate medications at hospital discharge and whether they differ by race, sex, and region, and the effect on mortality has not recently been explored in a large contemporary and diverse population. In ARIC manuscript proposal 1490, Dr. Patricia Chang et al. proposed to study the utilization of appropriate medical therapy for individuals with acute decompensated heart failure, the relationship of the use of appropriate medical therapy to various demographic and clinical characteristics, and the relationship of medication utilization to clinical outcomes including mortality in the ARIC surveillance study. The research findings were presented as an abstract at the American Heart Association Epidemiology/Lifestyles Meeting in 2015 using the ARIC surveillance from 2005 to 2011. Their main findings were that the overall proportion of use of guideline medical therapy was about 50% for individual with heart failure with reduced ejection fraction, the use of beta blockers was 80%, but the use of other mortality reducing medications were lower than 50%. More importantly use of optimal therapies were associated with improved survival. This research has not yet been published.

We would like to expand the aims of this study to: (1) use all 10 years of ARIC surveillance data to examine the overall use of guideline recommended medical therapy for heart failure (2005 to 2014), (2) examine the annual trends in the use of guideline recommended medical therapy from 2005 to 2014, and (3) examine variations in the trends by demographic characteristics specifically race and sex. The current guidelines for the use of guideline recommended medical therapy have been in place since 1995. This research will be a unique opportunity to investigate both the overall use of appropriate medical therapy and whether there have been improvements over the last 10 years.

We have consulted with and received support from Dr. Patricia Chang regarding the addendum. Dr. Chang, the primary author of the original manuscript proposal #1490 has agreed to this addendum and will be the senior author on the future proposal. In addition, we have updated the proposal (attached) to 1490B entitled “Utilization of Optimal Medical Therapy for Hospitalized Heart Failure and outcomes: The ARIC Study (2005-2014).”
5. **Main Hypothesis/Study Questions:**
Among individuals with acute decompensated heart failure (ADHF) in the community:
- What was the frequency of heart failure medical therapy for individuals with heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and heart failure with unknown EF?
- What are the annual trends in the use of guideline recommended medical therapy from 2005 to 2014?
- Is there an overall difference, and a difference in the trends in the use of guideline recommended medications at discharge by race, age, sex, or region?
- Are differences in quality of care associated with 28-day and 1-year mortality among individuals with acute decompensated heart failure.

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 design:**
Combination of cross-sectional and survival analyses

**Study population:**
ARIC community surveillance participants hospitalized from 2005 to 2014 with adjudicated definite or probable ADHF.

**Inclusion criteria:**
Hospitalization with ADHF

**Exclusion criteria:**
- Ethnicity other than black or white
- Discharge to hospice
- In-hospital mortality

**Exposure:**
- Heart failure with reduced EF (EF<50%), Heart failure with preserved EF (≥50%), Heart failure with unknown EF.

**Outcome:**
- Medications at hospital discharge: ACEi or ARB, BB, AA, nitrates + hydralazine, and diuretics at discharge. Each of the discharge medications will be modeled as a categorical variable (yes vs. no), as well as a composite of the medications defined by three categories: (1) optimal therapy (BB, ACEI or ARB, +/- AA); (2) acceptable therapy (BB, hydralazine + nitrate, +/- AA); (3) nonoptimal therapy (diuretic only, other medication combinations).
- Heart failure outcomes: Mortality at 28 days and 1 year

**Other variables of interest:**
- Demographics: age at discharge, sex, race, year of hospitalization, region
- Anthropometric characteristics: height and weight at admission and discharge, blood pressure (systolic and diastolic) at admission and discharge, heart rate
- Lifestyle characteristics: current smoker, former smoker, excess alcohol use, illicit drug use
- Clinical characteristics: hypertension, diabetes, coronary heart disease, myocardial infarction, atrial fibrillation/flutter, COPD, end stage renal disease (dialysis), stroke or TIA, cancer, lowest ejection fraction, arrhythmia (atrial fibrillation, flutter), pulmonary hypertension. Other medications at discharge: diuretics, lipid lowering therapy, calcium channel blockers, antiplatelets, anticoagulation, antiarrhythmics
- Left ventricular ejection fraction, highest BNP, highest troponin, hemoglobin, last eGFR, lowest sodium, length of stay, depression
- Inpatient procedures: CABG, PCI, Valve surgery, Pacemaker, Defibrillator, transthoracic echo, right heart catheterization, coronary angiography, stress test

**Statistical analysis plan:**
- Baseline characteristics will be compared across categories of heart failure using chi-square tests and analysis of variance for categorical and continuous variables respectively.
- We will assess the proportion of use of heart failure medications by race, sex, region, HF type, and other clinical and demographic characteristics.
- We will assess overall differences by race/sex and HF type by Calendar year (2005-2010) then (2010-2014)
- We will estimate trends of medication using linear regression models of the percentage of individuals on optimal medical therapy over time. Test for deviation of linear trends and using splines and use category by calendar year
- We will estimate hazard ratio and 95% confidence intervals using Cox proportional hazard regression analysis to assess the association between the individual medications, and overall differences by race/sex and HF type by Calendar year (2005-2010) then (2010-2014)
- We will estimate trends of medication using linear regression models of the percentage of individuals on optimal medical therapy over time. Test for deviation of linear trends and using splines and use category by calendar year
- We will estimate hazard ratio and 95% confidence intervals using Cox proportional hazard regression analysis to assess the association between the individual medications, and optimal/acceptable/nonoptimal medications and the outcome death. Follow up begins at the day of discharge. We will account for factors associated with treatment patterns as covariates or using propensity score weighting.
- We will perform sensitivity analysis excluding individuals with heart rate < 60 beats per min, and eGFR <30 ml/min per 1.72m² and consider excluding individuals systolic blood pressure < 90 mmHg at discharge. We will perform additional sensitivity analysis using the cutoff of LVEF <35% as an additional definition for HFrEF. In addition in African Americans we will use the outcome of medications (1)optimal therapy (BB, ACEI or ARB, ISDN/Hydralazine +/- AA); (2) acceptable therapy (BB, hydralazine +ISDN or ACEI/ARB +/- AA); (3) nonoptimal therapy (diuretic only, other medication combinations).
- We will test for interaction between SES, race and medication utilization with time

**Limitations**
- EF not always available from hospital echocardiograms
- Lack of information on adherence
- Lack of information on allergy, intolerance or contraindication to guideline-recommended medication
- Residual confounding
- Regional differences may not reflect racial differences (most African Americans came from the Jackson site)

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)?

1881(Blecker) Quality of care for hospitalized patients with chronic heart failure. The Atherosclerosis Risk in Communities (ARIC) Surveillance Study. The study population was the ARIC cohort; Dr. Chang and Dr. Rosamond were coauthors (and are part of this writing group).

MS 1325 (Foraker) Socioeconomic, demographic and clinical predictors of heart failure care: ARIC Cohort. The study population was the ARIC cohort, using ARIC visit data from baseline to 2004 and focused primarily on SES; Dr. Chang and Dr. Rosamond were coauthors.

MS 1951 (Sueta) Predictors of medication adherence after hospitalization for heart failure in ARIC. This study focused on CMS claims data; Dr. Chang was a coauthor.

MS 2043 (Rodgers) Predictors of Medication Adherence in Cardiovascular Disease: Understanding the Complex Relationships Between Disease Burden, Health Literacy, and Socioeconomic Status. The study population was the ARIC cohort, focused on medication adherence and health literacy at Visit 5; Dr. Chang was a coauthor.

MS 2554 (Rodgers) Impact of Initiation and Discontinuation of Guideline Directed Medical Therapy on Mortality in Patients Hospitalized with Heart Failure. While the study population was ARIC community surveillance, the focus was initiation, discontinuation, and maintenance of HF medications during the hospitalization, and did not specifically examine the effect of race/sex on the relationship of medication use and survival. This analysis used multiple imputation methodology for cases with missing LVEF; we will not be using this method. Dr. Chang was a coauthor.

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.cscucc.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:


5. Shah B, Hernandez AF, Liang L, Al-Khatib SM, Yancy CW, Fonarow GC, Peterson ED, and Get With The Guidelines Steering C. Hospital variation and characteristics of implantable cardioverter-defibrillator use in patients with heart failure: data from the GWTG-HF