1. **Full Title**: Impact of Initiation and Discontinuation of Guideline Directed Medical Therapy on Mortality in Patients Hospitalized with Heart Failure.  
   **Abbreviated Title (Length 26 characters)**: GDMT in HF

2. **Writing Group**: Eliza Daubert, Jo Ellen Rodgers, Carla Sueta, Patricia Chang, Sally Stearns, Anna Kucharska-Newton, Orly Vardeny, Khalid Alburikan, and Richard Tran; others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.

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3. **Timeline**: Data analyses will occur between May-September 2015 with anticipation of submitting an abstract to the American College of Cardiology on October 27, 2015. Manuscript will follow.

4. **Rationale**:  
Heart failure (HF) is a chronic disease state that affects 5.8 million Americans. Many of these patients experience one or more episodes of acute decompensated HF (ADHF) requiring inpatient care and leading to more than 1 million hospitalizations annually. These hospitalizations lead to an increased one year mortality rate after discharge of 20% to 30% and are associated with an annual cost to the US healthcare system of $37 billion. A subset of patients hospitalized with ADHF experience worsening HF, typically defined as persistent or worsening signs and symptoms requiring an escalation of therapy. Recently, Devore et al. found WHF to be associated with higher rates of mortality, rehospitalization, and cost. These investigators defined WHF as requiring one or more of the following: initiation of inotropic medications or an intravenous vasodilator more than 12 hours after hospital presentation, transfer to the intensive care unit after the first inpatient day, or initiation of advanced medical therapy (i.e. mechanical circulatory support, mechanical ventilation, or hemodialysis) after the first inpatient day. To date, the frequency and impact of discontinuation of guideline directed medical therapy (GDMT), including angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), beta blockers (BBs), digoxin, aldosterone receptor antagonists (ARAs), and hydralazine/isosorbide dinitrate, in the setting of WHF has not been evaluated.
Several studies have investigated the effects of initiating GDMT in patients hospitalized for ADHF. Registry and biomarker data support that initiation of an ARA prior to discharge reduces readmission rates; however, the effect on mortality remains unclear\textsuperscript{10,11}. Outcome data have also demonstrated that BB initiation significantly reduces both short and long term mortality although no change in readmission rate was observed\textsuperscript{12}. Results from the Alabama Heart Failure Project indicate digoxin reduces all-cause readmission at both 30 days and one year post-discharge in patients with a reduced ejection fraction; however, impact on patients with preserved ejection fraction has not been demonstrated\textsuperscript{13}. No studies have evaluated the impact of discontinuation of GDMT on outcomes.

An ARIC manuscript currently in draft by Chang et al, estimates the rates of use of optimal medical therapy (BB plus ACEI/ARB with or without an ARA), acceptable therapy (BB plus hydralazine/isosorbide dinitrate with or without an ARA), and nonoptimal therapy (diuretic only or any other mutually exclusive combination of medications) based on demographics, regional differences, health insurance status, and comorbidities\textsuperscript{14}. Chang et al will also examine the relationship between the use of optimal therapy and clinical outcomes such as mortality\textsuperscript{14}. Importantly, these investigators assessed therapy on discharge alone and not change in therapy from admission to discharge.

This manuscript will build on the work of Chang et al by investigating the baseline characteristics (e.g., chronic kidney disease, respiratory disease) which predict the discontinuation of GDMT during hospitalization and the impact of initiation and discontinuation of GDMT during hospitalization on mortality. Importantly, unlike the work of Chang et al, each GDMT will be assessed individually given that the predictors of initiation and discontinuation may vary with individual agents. For example, chronic kidney disease may lead to discontinuation of ACEI/ARBs or digoxin and ARAs. Airway disease, diabetes mellitus, or depression may lead to discontinuation of BBs. Finally, hypotension or bradycardia may lead to the discontinuation of several GDMT. This study will include approximately 4000 subjects from the ARIC non-cohort community HF hospitalization surveillance data. Data from the ARIC non-cohort community surveillance sample will be utilized to compare patients in whom GDMT was discontinued to those in whom it was continued. Outcomes to be assessed will be mortality with the goal of providing practitioners with additional evidence on which to base WHF treatment decisions.

5. Study Objectives:

The study will address the following objectives:

1. To determine what baseline characteristics predict initiation and discontinuation of GDMT in patients hospitalized with HF. Importantly, each GDMT will be assessed individually.
2. To determine the impact of initiation and discontinuation of GDMT during hospitalization on post-discharge mortality in patients hospitalized with HF. Again, each GDMT will be assessed individually.

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:

Data: ARIC Community HF Hospitalization Surveillance Records

Inclusion criteria:

1) Hospitalization for HF due to ADHF or other reasons (e.g., COPD)
2) Chronic HF prior to admission with reduced ejection fraction (HFrEF, LVEF ≤ 40%) or preserved ejection fraction (HFpEF, LVEF ≥ 41%)

Exclusion criteria: In-hospital deaths and patients discharged to hospice.

Comparator groups:
- Initiation of GDMT* vs no initiation of GDMT during hospitalization among patients not receiving GDMT prior to hospitalization
- Discontinuation of GDMT* vs continuation of GDMT during hospitalization among patients receiving GDMT prior to hospitalization

*GDMT = ACEI/ARB, BB, digoxin, ARA, hydralazine/isosorbide dinitrate

Predictors:
Predictors of discontinuation of GDMT to be investigated are listed in the table below which also provides data origin.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Origin of Data</th>
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<tbody>
<tr>
<td>Age</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Ethnicity/Race</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Worst/Last Value</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Ejection Fraction</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Serum Creatinine</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Blood Urea Nitrogen</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Hemoglobin</td>
<td>Hospital Admission/Event Onset</td>
</tr>
<tr>
<td>Brain Natriuretic Peptide (BNP)</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Pro-Brain Natriuretic Peptide (pro-BNP)</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Troponin T</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Sodium</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Asthma</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Chronic Kidney Disease</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Coronary Heart Disease</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Hypertension</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Atrial Fibrillation/Flutter</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Depression</td>
<td>Hospital Admission/Event Onset</td>
</tr>
<tr>
<td>Discharge to hospice</td>
<td>Hospital Admission/Event Onset</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>Hospital Admission/Event Onset</td>
</tr>
<tr>
<td>Asthma</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Chronic kidney disease</td>
<td>Hospital Admission/Event Onset</td>
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<tr>
<td>Coronary heart disease</td>
<td>Hospital Admission/Event Onset</td>
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<td>Diabetes mellitus</td>
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<tr>
<td>Discharge to hospice</td>
<td>Hospital Admission/Event Onset</td>
</tr>
</tbody>
</table>

These predictors will be assessed collectively for the entire study sample.

Outcomes:
1. Mortality at 1 year (estimated with logistic regression)
2. Time to death (estimated with Cox proportional hazard)

Outcomes will be assessed both collectively for the entire study sample and separately for HFrEF and HFpEF subgroups.

Analytical methods:
Descriptive statistics for possible predictors of discontinuation will be compared for the comparator groups using appropriate statistical tests based on the distribution of the predictor variable (e.g., t-statistic for continuous variables, Chi-square for dichotomous categorical variables). Predictors will include age, gender, ethnicity, pulmonary disease including asthma and chronic obstructive pulmonary disease, chronic kidney disease, coronary heart disease, diabetes, hypertension, atrial fibrillation/flutter, depression, as well as physical exam and/or laboratory findings on admission including blood pressure, heart rate, ejection fraction, serum creatinine, sodium, BNP/pro-BNP, troponin T, and hemoglobin.

We will use logistic regression to estimate models of GDMT discontinuation as a function of the predictors in the table; two models will be estimated separately for hospitalizations based on whether the patient was recorded as being on GDMT at time of admission. Since treatment and comparator groups usually differ in underlying characteristics due to treatment selection, we will
estimate propensity score weights from these logit models. The PS weights will then be used for inverse propensity score weighting of our outcome models: a logistic model for whether the patient dies within one year of discharge, and a Cox proportional hazards model for time to death. All models will also be adjusted using weights as appropriate to reflect the sampling probability for the observations.

One limitation of the ARIC community hospital surveillance data for HF hospitalizations is that multiple hospitalizations for the same person are not identified either within or between hospitals. Even though ARIC only samples approximately 20% of HF hospitalizations (the actual sampling fraction varies by selected patient characteristics), some observations may pertain to the same patient. This lack of independence between some observations means the estimated standard errors will be smaller, but we will not be able to determine the extent to which the precision is overestimated.

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 ____ X___ 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
   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”? ____ X___ Yes ____ X___ 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.cscn.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)?
    This manuscript is related but our proposal seeks to further build on this work.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _____ X___ No
   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/

12. a. 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.
   b. 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.
13. References:


