

ARIC Manuscript Proposal #3422

PC Reviewed: 6/18/19
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: The association of race and socioeconomic differences in medication utilization and outcomes for individuals with acute decompensated heart failure in the community (ARIC Cohort).

b. Abbreviated Title (Length 26 characters): Differences in heart failure quality of care

2. Writing Group:

Writing group members: Lena Mathews, Yejin Mok, Jung-Im Shin, Deidra Crews, Wayne D. Rosamond, Patricia P. Chang, Chiadi Ndumele, Josef Coresh, Kunihiro Matsushita, (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

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: **Kunihiro Matsushita**

Address: Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health,
2024 E. Monument St., Suite 2-600 (Rm 2-602), Baltimore, MD
Phone: (443) 287-8766 Fax: (410) 367-2384
E-mail: kmatsush@jhsph.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), a syndrome of impaired heart filling or ejection of blood, affects 6.5 million people in the US.¹ A growing public health challenge, HF prevalence will increase by 46% by the year 2030.² HF is associated with substantial morbidity, mortality, and healthcare costs, with a 1-year mortality rate of 30% after diagnosis.¹⁻³ Medical therapies blocking

neurohormonal activation and adverse ventricular remodeling have shown a significant prognostic benefit in HF with reduced ejection fraction (HFrEF).⁴⁻¹⁵ Consequently, the implementation of these guideline-recommended medical therapies (GDMT) in patients with HFrEF has resulted in declines in HF mortality rates in the US.^{3, 16}

Racial disparities in HF outcomes exist. For example, black patients develop more HF from preventable causes like hypertension and obesity compared with white patients.^{17, 18} Black and Hispanic patients with HF report worse symptoms, functional status, and quality of life.¹⁹ Furthermore, black patients have a higher incidence of HF at younger ages (<40 years)^{17, 20} and black males have the highest incidence of HF across all ages and racial groups.²¹ In the ARIC Surveillance of four US communities, there was a significant increase in longitudinal trends in hospitalizations for acute HF among black men and women compared with white participants.³ Moreover, in the ARIC Cohort, after hospitalization with HF, black patients had a significantly higher 5-year case fatality rate compared with white patients.²²

In this context, research has shown that a substantial number of HFrEF patients are not treated with GMT for HF.²³⁻²⁸ However, only a few studies have examined racial differences in GMT use in HF and have obtained conflicting results.^{29,30} Of note, these few studies explored very different settings, small single-center studies and hospitals involved in voluntary quality improvement initiatives³¹ and thus may not be widely generalizable to real world populations.

Moreover those previous studies did not explore whether socioeconomic status (SES) including individual level characteristics such as income level, education attainment; and neighborhood characteristics such as the area deprivation index (ADI), a measure of socioeconomic deprivation of a geographic area, may explain racial disparities in HF outcomes.³⁴ Individuals with low SES may be less likely to refill prescribed medications, attend follow up appointments, seek medical attention when symptoms develop, and have the insight into the management of their disease.

Our objective is to explore the utilization of GDMT for HF at hospital discharge and its impact on outcomes by race and SES. We will explore these questions in the ARIC cohort because of the extensive adjudication of heart failure events, information on socioeconomic status, comorbidities, and outcomes including re-hospitalization and mortality.

5. Main Hypothesis/Study Questions:

Aim 1: To determine differences in utilization of GMT for HFrEF at hospital discharge by race in the ARIC Cohort. We postulate that black race will be associated with lower utilization of GDMT at discharge in individuals hospitalized with acute decompensated HFrEF.

Aim 2: To evaluate the association between the use of GDMT and HF outcome of mortality and repeat hospitalization by race. We postulate the use of GDMT will be associated with reduced mortality and repeat hospitalization, and that racial differences in GDMT use will correlate with racial differences in HF rehospitalization.

Aim 3: To evaluate whether SES contributes to racial differences in HF GDMT utilization as well as the adverse outcomes of mortality and repeat hospitalization. We postulate that SES will partially explain the racial differences in HF GDMT and outcomes of mortality and repeat hospitalization.

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 (during incident ADHF hospitalization) and prospective cohort (after incident ADHF hospitalization) study

Study population:

ARIC cohort participants hospitalized from 2005 to 2017 with adjudicated definite or probable ADHF.

Inclusion criteria:

Hospitalization with adjudicated ADHF with reduced ejection fraction (EF<50%).

Exclusion criteria:

We will exclude races that are other than black and white. We will also exclude black participants from the Minneapolis and Washington County field centers. We will also exclude those discharged to hospice or who die prior to discharge.

Exposure, outcome, and statistical analysis: Summarized by aims below

Other variables of interest:

-Demographics: age at discharge, sex, race, year of hospitalization, region of hospitalization

-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, chronic obstructive pulmonary disease, stroke or transient ischemic attack cancer, lowest ejection fraction, arrhythmia (atrial fibrillation, flutter), pulmonary hypertension. Other medications at discharge: diuretics, lipid lowering therapy, calcium channel blockers, antiplatelet, anticoagulation, antiarrhythmic

-Other variables: Left ventricular ejection fraction, highest b-natriuretic peptide (twice upper limit of normal vs below), highest troponin (twice upper limit of normal vs below), hemoglobin, last eGFR, lowest sodium, length of stay, depression

(a) Aim 1: To determine differences in utilization of GDMT for HF rEF at hospital discharge by race in the ARIC Cohort.

Exposure: Race categorized as (black vs. white).

Outcome: Each GDMT therapy as a binary variable: ACE inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) (yes /no), β -blockers (BB) (yes/no), Aldosterone antagonist (AA) (yes/no), Hydralazine and Nitrates (ISDN/H) (yes/no); or as a combination (1) Optimal therapy (ACE/ARB + BB, +/- AA, +/- ISDN/H) (2) Adequate therapy (BB only, ISDN/H only, ACE or ARB only, AA only) (3) Inadequate therapy (no HF therapies). In secondary analysis we will also assess for utilization of inpatient procedures including coronary artery bypass graft, percutaneous coronary intervention, valve surgery, pacemaker/defibrillator, transthoracic echo, right heart catheterization, coronary angiography, stress test during

Statistical analysis: Cross sectional analysis

- Descriptive statistic of key GDMT by race
- Logistic regression to estimate the adjusted odds ratio of each GDMT and procedure by race. We will also assess whether other clinical factors including eGFR <30 ml/min per 1.73m², blood pressure <90 mmHg, heart rate < 60 bpm are associated with the use of guideline recommended therapy.

- The regression models will be adjusted for demographics, lifestyle and clinical characteristics.

(b) Aim 2: To evaluate the association between the use of GDMT and HF outcome of mortality and repeat hospitalization by race.

Exposure: Each GDMT therapy as a binary variable: ACE inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) (yes /no), β -blockers (BB) (yes/no), Aldosterone antagonist (AA) (yes/no), Hydralazine and Nitrates (ISDN/H) (yes/no); or as a combination (1) Optimal therapy (ACE/ARB + BB, +/- AA, +/- ISDN/H) (2) Adequate therapy (BB only, ISDN/H only, ACE or ARB only, AA only) (3) Inadequate therapy (no HF therapies).

Outcome: Mortality and re-hospitalization with ADHF.

Statistical analysis: Prospective analysis

- Cox proportional hazard analysis to assess the longitudinal association between each GDMT individually and in combination on the outcome mortality and re-hospitalization.
- We will stratify the results by race.
- The regression models will be adjusted for demographics, lifestyle and clinical characteristics.
- We will also estimate propensity score weights using logistic regression with characteristics that are known to be related to the exposure of GDMT and the outcome. We will use propensity score for inverse probability weighting of our regression models.

(c) Aim 3: To evaluate whether SES contributes to differences in HF GDMT utilization as well as the adverse outcomes of mortality and repeat hospitalization.

Exposure: Socioeconomic status measured at visit 1: separately and as a composite score. Household income at visit 1 will be categorized into three levels (<\$12,000, \$12,000-\$24,999, >\$25,000). Educational attainment at visit 1 will be categorized into three levels (< high school, high school or equivalent, > high school). Area deprivation index (ADI) measured at visit 1 will be categorized into five equal quintiles.

Outcome: Mortality and re-hospitalization with ADHF.

Statistical analysis: Combination of cross-sectional (GDMT utilization) and prospective analysis (mortality and repeat hospitalization)

- Descriptive statistic of key GDMT by SES status
- Logistic regression to estimate the adjusted odds ratio of each GDMT and procedure by SES. We will also assess whether other clinical factors including eGFR <30 ml/min per 1.73m², blood pressure <90 mmHg, heart rate < 60 bpm are associated with the use of guideline recommended therapy.
- The regression models will be adjusted for demographics, lifestyle and clinical characteristics.
- Cox proportional hazard analysis to assess the longitudinal association between each GDMT individually and in combination on the outcome mortality and re-hospitalization by SES status (individual components and composite score)
- The regression models will be adjusted for demographics, lifestyle and clinical characteristics. We will test for interaction between SES, race and medication utilization
- In sensitivity analysis, we will also estimate propensity score weights using logistic regression using with characteristics that are known to be related to the exposure of

guideline-recommended therapy and the outcome. We will use propensity score for inverse probability weighting of our regression models.

Limitations

- Residual bias by indication associated with the exposure and outcome and not captured by measured predictors.
- EF is not always available from current hospital echocardiograms and they may be variability in accurate assessment of EF from other imaging modalities
- Lack of information on allergy, intolerance or contraindication to guideline-recommended medication
- Residual confounding
- Lack of information on adherence after hospitalization
- 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.csc.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)?

1490 (Chang)Utilization of optimal medical therapy for hospitalized heart failure and outcomes: the ARIC Surveillance Study. (1) The primary author is a co-author on the proposal. (2) We would like to perform the analysis in the Cohort study and look at repeat hospitalizations and the effects of socioeconomic status which are not available in the Surveillance study.

216 (Lewis) Changes in utilization of cardiovascular medication in the ARIC study (1) This paper uses data from 1994

1881(Blecker) Quality of care for hospitalized patients with chronic heart failure. The Atherosclerosis Risk in Communities (ARIC) Surveillance Study. (1) This proposal was in the Surveillance study (2) Focused on ACE/ARB and evaluation of LV function (3) Dr. Chang and Dr. Rosamond were coauthors (and are part of this writing group) (4) Did not focus on race/SES

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

2257(Kucharska-Newton) Patterns of healthcare utilization following an initial diagnosis of heart failure. The Atherosclerosis Risk in Communities (ARIC) Study (1) This study did not focus on medications

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.csc.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.csc.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.

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