ARIC Manuscript Proposal #2051

PC Reviewed: 12/11/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Prevalence and prognostic impact of kidney dysfunction among patients with acute decompensated heart failure in community setting: ARIC Community Surveillance

b. Abbreviated Title (Length 26 characters): Kidney dysfunction in HF

2. Writing Group:

Writing group members:
Kunihiro Matsushita, Sunil K. Agarwal, Laura Loehr, Hanyu Ni, Josef Coresh, Patricia P. Chang, Wayne Rosamond, others are welcome to join

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

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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).
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3. Timeline: Analysis to begin winter 2012/2013, with abstract to be completed by June 2013 (will be submitted for AHA in November, 2013), and manuscript by summer 2013.

4. Rationale:

Kidney dysfunction is a strong predictor of adverse health outcomes in a broad range of populations.[1-6] Patients with heart failure are not exception, and numerous studies have

reported that lower kidney function is associated with poor prognosis in patients with heart failure in both outpatient and inpatient settings.[7-21] However, generalizability of those data to clinical practice in community is limited as many of these reports are from clinical trials with stringent inclusion criteria,[7-16] and most of the others are data from a single hospital (usually large hospitals).[17-19] Thus, the prevalence of kidney dysfunction or its prognostic utility from a community based sample of hospitalized heart failure is missing. Though a report from a large registry study in the US may reflect community setting,[20,21] registry studies have some caveats related to their property for arbitrary data entry.[22] Also, only a few of above studies have used a measure of kidney dysfunction as recommended in clinical guidelines, i.e., estimated glomerular filtration rate (eGFR).

Therefore, the main objective of this study is to evaluate the prevalence of kidney dysfunction assessed by the latest eGFR equation using serum creatinine (CKD-EPI equation)[23,24] and its prognostic impact among patients who were hospitalized for acute decompensated heart failure (ADHF) in community hospitals using the community surveillance data from the Atherosclerosis Risk in Communities (ARIC) Study with case adjudication by experts.[25] This study will provide a unique opportunity to assess whether those estimates vary across subgroups according to age, sex, race, status of hypertension and diabetes, and HF type (reduced vs. preserved ejection fraction [EF]). Also, we will evaluate whether HF treatment differs by kidney dysfunction among patients with ADHF in community hospitals.

5. Main Hypothesis/Study Questions:

1. What is the prevalence of kidney dysfunction in patients hospitalized with ADHF in community settings overall and in key subgroups according to age, sex, race, status of hypertension and diabetes, and HF type?
2. Among those with ADHF, is kidney dysfunction independently associated with in-hospital, 28-day, and 1 year mortality overall and in key subgroups according to age, sex, race, status of hypertension and diabetes, and HF type?
3. Among those with ADHF, does HF treatment (diuretics, inotropes, renin angiotensin system inhibitors [RASI], etc.) during hospitalization and at discharge differ by kidney function overall and in key subgroups according to age, sex, race, status of hypertension and diabetes, and HF type?

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).

We will use data abstracted from HF medical records from the ARIC Community Surveillance, and all definite or possible ADHF cases adjudicated from 2005 onward by the ARIC HF committee with linkage to the National Death Index (for case fatality) will be included in this analysis. All analyses will be weighted by sampling fractions specific to each of the ARIC communities, accounting for population size, sex, and race. Demographic and clinical variables of interest will include age, sex, race, history of heart failure (diagnosis, prior hospitalization, or treatment), heart failure type (i.e., reduced vs. preserved ejection fraction [EF]), length of hospital stay, in-hospital, 28-day and 1 year

mortality, serum creatinine, blood urea nitrogen, serum sodium, height, body weight, hemoglobin, hematocrit, history of renal disease (dialysis), smoking, blood pressure, diabetes, chronic obstructive pulmonary disease (COPD), history of coronary disease, and health insurance status.

As recommended in clinical guidelines, kidney function will be primarily evaluated by eGFR. The CKD-EPI equation incorporating age, sex, race, and serum creatinine will be used. eGFR will be treated as a continuous variable with splines as well as categories defined in clinical guidelines (<15, 15-29, 30-44, 45-59, 60-89, and ≥90 ml/min/1.73m^2). eGFR <60 ml/min/1.73m^2, CKD stage 3 to 5, will be considered as kidney dysfunction. Worst (highest) and last measurements of serum creatinine during hospitalization are available, and we will repeat our analysis for both measures. However, our primary analysis will use worst serum creatinine, since this reflects both baseline kidney function and its alteration during hospitalization and hence would carry more prognostic information than the other measure determined by timing (i.e., last measurement).[26-28] Given that blood urea nitrogen was a stronger predictor of poor prognosis than serum creatinine in some studies,[20,21] we will also test blood urea nitrogen as well as serum creatinine as a measure of kidney function.

Prevalence of CKD stage 3-5 will be estimated among ADHF cases, and prevalence odds ratios by age, sex, race, and HF type will be calculated. The prevalence of kidney dysfunction will be assessed after stratifying by covariates of interest, and compared by χ^2 test. We will also assess the proportion of kidney dysfunction ameliorating during hospitalization (those with eGFR <60 ml/min/1.73m^{2}with highest serum creatinine but ≥60 with last serum creatinine) and explore clinical factors associated with the recovery of kidney function.

Associations between kidney dysfunction among HF patients and mortality (in-hospital, 28-day and 1 year) will be demonstrated in Kaplan-Meier survival curves and will be examined by Cox proportional hazards models as well as logistic regression, after controlling for potential confounders such as age, sex, race, diabetes, hypertension, smoking, COPD, serum sodium, history of coronary heart disease, and ejection fraction. We will assess whether prognostic information of kidney dysfunction differs by age, sex, race, status of hypertension and diabetes, and HF type by stratified analysis and models incorporating interaction terms between these factors and kidney function.

Subsequently, we will evaluate whether the use of HF treatment during hospitalization and at discharge differs by kidney dysfunction. HF treatment of interest would include diuretics, inotropes, RASI, and beta blockers. Odds ratio for the use of these medications will be evaluated by kidney function after accounting for potential confounders.

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.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)?
#1118: Reduced Kidney Function as a risk factor for incident heart failure: The ARIC Study; Kottgen, A

*There are no proposals investigating the association of kidney dysfunction with mortality among those with ADHF using ARIC Surveillance data.

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.

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