1.a. Full Title:
Predictive value of changes in BNP, Troponin, Hemoglobin and Serum Sodium in patients with acute decompensated heart failure

b. Abbreviated Title (Length 26 characters): BNP, Tn, Hb and sodium in ADHF

2. Writing Group:
Writing group members:

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

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3. Timeline:
Manuscript will be written and submitted for publication within one year of initiation of analysis.

4. **Rationale:**
It is estimated that heart failure (HF) affects over 6 million people in the United States (1) and is responsible for approximately two million hospitalizations annually. Diagnosis of acute decompensated heart failure (ADHF) is generally based upon symptoms and signs in addition to measurement of B-type natriuretic peptides to help rule out other causes of acute dyspnea. The sensitivity of BNP for diagnosis of HF is around 90% with a specificity of 74% (2). However, lower values for BNP are found in heart failure with preserved ejection fraction (HFpEF) patients (3-6); with about 30% HFpEF patients reportedly having a normal BNP (7).

It has been widely shown that higher BNP (8,9) and troponin levels (10-12) are poor prognostic indicators, with some studies combining the two for better prognostic value (13,14). A recent Korean study (15) demonstrated a 2-fold increase in mortality in patients with BNP in the highest quartile on admission. In a substudy of the COPERNICUS trial (16), higher NT-proBNP on admission was also associated with increased risk for all cause mortality in patients with severe HFrEF. Studies have also been conducted looking at the benefit of reduction in BNP levels during hospitalization indicating better outcomes (17- 21). However, the vast majority of the studies to date are in patients with a reduced ejection fraction and few classify results by variation in EF.

Anemia is another common finding in patients with advanced heart failure, though studies differ in their prognostic findings. Some studies have shown anemia in ADHF to be associated with poorer outcomes (22-24) without significant difference for in-hospital mortality between HFrEF and HFpEF (25). Others have shown no effect of anemia on outcomes (26). In addition, serum sodium is well studied as a prognostic marker, with hyponatremia being documented as a poor prognostic indicator (27,28). However, in both cases, few studies investigate the effect of changes in levels of these markers on outcomes, much less on HFpEF compared to HFrEF.

The ARIC HF surveillance offers an opportunity to utilize the data collected to investigate if absolute as well as relative (as compared to worst levels) levels of above biomarkers at discharge provide prognostic information among patients admitted with ADHF, both with reduced and preserved EF.

5. **Main Hypothesis/Study Questions:**
   a. To examine the prognostic value of changes in cardiac biomarkers (BNP/NT-pBNP, Troponin I/TroponinT), hemoglobin, and serum sodium, both separately
and in combination, on 28 day and 1 year mortality in patients hospitalized with ADHF.
b. To compare the prognostic value of changes in cardiac biomarkers to the prognostic value of last values and worst values on 28 days and 1 year mortality in patients hospitalized with ADHF.
c. To examine how the prognostic value of changes in biomarkers vary by gender, age, race, ejection fraction (HF type), and select comorbidities (including chronic kidney disease, and obesity).
d. To examine the correlation between BNP, Troponin, hemoglobin and serum sodium in HFpEF patients compared to HFrEF patients.
e. In the subset of patients who are followed in the ARIC cohort study, to examine the predictive value of changes in biomarkers on rehospitalization rates for ADHF, according to gender, age, race, heart failure type, and select comorbidities.

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, Inclusion/Exclusion:
This study will include hospitalized patients from the ARIC community surveillance study with a validated diagnosis of ADHF. At present, data is available for analysis from the year 2005 to 2011. Patients will be categorised according to HF type: ejection fraction greater than 50% (HFpEF) or less than 50% (HFrEF). The small number of participants with a recovered EF will be classified as HFrEF, given that they had a documented reduced EF in their history. Those without a documented EF will be excluded in the primary analysis. Those with a documented diagnosis of MI/ACS during admission will be excluded from the troponin dataset. The ADHF rehospitalization rates will be obtained from Cohort study data.

Outcomes:
All outcomes will be analysed according to HF type:
1. Changes in biomarkers during admission for ADHF.
2. 28 day and 1 year mortality after admission for ADHF.
3. Variation in predictive value by gender, race, age and HF type.
4. Correlation between measured biomarkers during ADHF admission.
5. Rehospitalization rates for ADHF.

Variables of Interest:
a. BNP/NT-pBNP (last and worst during hospitalization)
b. Troponin I and T (last and worst during hospitalization)
c. Serum Sodium (last and worst during hospitalization)
d. Ejection Fraction: current and past
e. HF type (HFpEF, HFrEF or recovered HFrEF)
f. Demographics/clinical characteristics:
   a. Gender
   b. Race (classified by gender)
   c. Age
   d. BMI (using last recorded weight)
   e. Prior hospitalization for heart failure
   f. Heart Rate at presentation
   g. Systolic and diastolic blood pressure at presentation
   h. Serum creatinine, Serum BUN, estimated glomerular filtration rate
   i. Hemoglobin level
   j. Coronary Heart Disease/Hx of MI
   k. Atrial Fibrillation/Atrial flutter
   l. Hypertension (SBP > 140, DBP > 90 or medication use)
   m. Valvular heart disease
   n. COPD (PFTs demonstrating obstructive disease, use of inhaler for COPD, evidence on imaging)
   o. Dialysis (current therapy only)
   p. Diabetes (Type I or Type II)
   q. Symptoms and signs of excess volume (e.g., edema, dyspnea, PND, orthopnea, rales, JVD)

**Summary of Data Analysis:**

- Descriptive statistics. (1) The distribution of worst value, last value, and change in BNP, Tn, sodium and hemoglobin. Categorization of each biomarker will be based on its respective distribution (by change from last value to worst value and divided into defined categories within this distribution range). (2) Demographic and clinical characteristics according to the distribution of each biomarker category (presented in above mentioned categories). (3) Correlation of BNP and Tn (and other combinations) by worst value, last value, and change (3 correlations for each pair).

- Kaplan Meier curves for mortality according to BNP, Tn, sodium, hemoglobin, and then combined BNP/Tn (by worst value, last value, and change).

- Logistic Regression to assess the effect of changes of biomarkers (contribution of BNP, Tn, sodium, hemoglobin, and then combined BNP/Tn) on case fatality at 28
days and 1 year, adjusting for potential confounders (such as factors contributing to changes in BNP such as obesity and CKD).

- Multivariate Cox proportional hazards models to assess the effect of changes of biomarkers on ADHF rehospitalization in the subgroup who are ARIC cohort participants.

**Limitations:**
The admission value of these biomarkers are lacking; thus, by design, by having only worst and last values, we can only assess the impact of improvement vs. no change. Moreover, the total number of biomarker measurements during the hospitalization is unknown. The vast majority of measurements of natriuretic peptides are BNP (>70%), and the vast majority of troponin measurements are troponin I (>90%). We, therefore, can use the percentage change in BNP and NT-proBNP, and in troponins I and T, to overcome this limitation if both biomarkers are to be combined. Finally, there are certain care characteristics which impact prognosis and mortality in HF and cannot be assessed; e.g., medication compliance.

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.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)?
   a. #2061, Deswal A et al. BNP as a prognostic marker in obese ADHF
   b. #1551, Agarwal et al. Characteristics and outcomes of patients with HFpEF
   c. #1946, Caughey et al. Prevalence and outcomes of anemia in ADHF
   d. #2051, Matsushita et al. Prevalence and prognostic impact of kidney dysfunction among patients with ADHF in community setting.
   e. Recently submitted (# pending), Sharma et al. Race and Gender Differences in Heart Failure with Preserved Ejection Fraction: Morbidity, Case Fatality, and their Determinants

Authors from the writing group of most of these proposals are involved in the current writing group.

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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Acute Heart Failure (From the Korean Heart Failure [KorHF] registry). (pending publication)


