ARIC Manuscript Proposal #2061

PC Reviewed: 1/9/13 **Status: <u>A</u>** **Priority: <u>2</u>**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1. a. Full Title:
"BNP as a prognostic marker in obese patients with acute decompensated heart failure and preserved ejection fraction"

 b. Abbreviated Title (Length 26 characters): BNP in obesity and HFpEF

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

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3. Timeline:

Manuscript to be written and submitted for publication within one year of initiation of analysis

4.   **Rationale**:

The prevalence of obesity has reached unprecedented proportions in the United States, with an estimated 300,000 deaths attributed to obesity every year [1]. It has been linked to multiple risk factors for cardiovascular diseases, including hypertension, diabetes, dyslipidemia and heart failure (HF) [2-4]. Heart failure with preserved ejection fraction (HFpEF) may constitute ~ 50% of all HF patients in the community and is more common in female, obese and elderly patients. HFpEF is characterized by symptoms of HF in the presence of a normal or relatively normal left ventricular ejection fraction ($\geq$ ~ 50%) [5]. B-type natriuretic peptide (BNP) is a known biomarker in clinical practice to assist in HF diagnosis and assessment of prognosis [6-8]. Although BNP has been shown to independently predict survival in patients with HF, the following two groups of patients may have variation in the diagnostic and prognostic usefulness of BNP: 1) obese 2) HFpEF [9-12].

Studies have shown that although overall patients with HFpEF have elevated levels of BNP, they are usually significantly lower than those with HF and reduced ejection fraction (HFrEF) and may even be normal in some of these patients [9, 13-15]. Several studies have investigated the relationship between BNP and obesity [11, 16-20] as well as between obesity and NT-proBNP [21-25]. With the exception of one [22], all studies have shown an inverse relationship between BMI and BNP. Moreover, an interventional study of 22 patients showed an increase in BNP levels after bariatric surgery resulted in BMI reduction [12], suggesting a bidirectional link between BMI and BNP.

Several mechanisms have been put forward to explain this inverse correlation between BNP and obesity. Increased expression of NP clearance receptors (NPR-C) in obese individuals may facilitate remove of BNP from the circulation [17-20, 25]. To further strengthen this concept, increased NPR-C gene expression has been shown in adipose tissue in humans [26]. However, pro-BNP has also been inversely associated with obesity, and does not show increased clearance through NPR-C receptors, suggesting that there may be other mechanisms involved [27]. Another explanation is related to impaired synthesis or secretion of BNP from the myocardium [28, 29]. Low BNP levels in obese patients may also just reflect a less advanced staged of HF compared to lean patients [17]. Finally, it may be a part of "cardiac cachexia", characterized by neurohumoral activation in HF leading to high BNP levels in lean patients compared to normal BNP levels in obese patients who tend to have a better metabolic reserve [30, 31].

BNP has been shown to predict outcomes in patients with HF independent of their ejection fraction (EF) [32]. However, most of the literature has focused on HF with reduced EF (HFrEF). Horwich et al [17] published a study of 316 clinic (outpatient) participants, showing that BNP independently predicted outcomes in all weight categories including the obese group, however, only patients with reduced EF were enrolled in this observational study. Christenson et al [33] studied 685 obese patients with

decompensated HF, and demonstrated that both BNP and pro-BNP are independent predictors of all-cause mortality in obese HF patients; however they did not subdivide the HF patients based on their EF. Frankenstein et al [34] studied the prognostic value of pro-BNP in chronic stable HF patients, and showed BNP to be an independent predictor of outcome in obese individuals. Two other studies, namely by BASEL group [35] and Bayes-Genis et al [36] further confirmed the prognostic significance of BNP in obese patients, however both studies looked at patients presenting with acute dyspnea in general, rather than specifically with HF. To the best of our knowledge, there has not been any study to date that addressed the prognostic value of BNP in obese patients with HFpEF. As mentioned above, both obesity and HFpEF are associated with relatively lower BNP levels and patients with HFpEF have a high prevalence of obesity. Therefore, it will be important to examine in detail the patterns of BNP elevation, as well the prognostic value of BNP levels in this specific patient population, as compared to patients with HFpEF without obesity as well as to patients with HFrEF. The findings of this study could inform clinical decision making in patients with HFpEF.

The Community surveillance for HF performed by the ARIC study offers a unique opportunity to address this question. Hospitalization records have been abstracted by trained abstractors; the abstracted data have then been examined by trained reviewers (with disagreements resolved by an adjudicator) to classify events as acute decompensated HF. Several variables including ejection fraction, BMI and BNP (or NT-proBNP in a smaller subset) are available in the chart-abstracted data for these patients.

5.   Main Hypothesis/Study Questions:

Study questions:
    a. To examine the distribution of BNP levels by BMI categories in patients with acute decompensated HF (ADHF) with HFpEF vs. HFrEF.
    b. To evaluate the prognostic value of BNP levels in ADHF on 1-year mortality in BMI categories in patients with HFpEF and compare it to HFrEF.

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 all patients with HF events coded as definite or possible ADHF for the years available in the HF surveillance data. Only patients with known left ventricular ejection fraction (LVEF) who have mortality data for one year follow-up, at the time the analysis is initiated, will be included. At present hospitalization data is available for 2005-2009; although mortality data is only available for 2005-2008 patients. All patients with HF will be categorized as having HFpEF (LVEF $\geq 50\%$) or HFrEF (LVEF $< 50\%$). The distribution of BNP levels and the prognostic utility of BNP will be assessed in both EF groups in four distinct weight categories based on the BMI: normal

weight, underweight, overweight and obese. It is possible that there may not be adequate numbers in the underweight categories, in which case those patients will be excluded from the analysis. If adequate numbers of patients are available, the obese patients will be divided into obese (BMI 30-39.99 kg/m2) and morbidly obese (BMI $\geq$ 40 kg/m2). In addition, subgroup analysis will be conducted in patients with and without atrial fibrillation because atrial fibrillation is independently associated with higher levels of BNP.

Variables of Interest:
   a) BNP (highest level and last value) during hospitalization; the majority of patients have BNP levels but a small group have NT pro-BNP levels.
   b) BMI (calculated using height and weight). Ideally we would like to use the weight at discharge as that may be closer to the dry weight (after treatment for HF), but we realize that fewer patients have weight data at discharge compared to admission. Therefore we will likely have to use admission weights to calculate BMI.
   c) Ejection fraction: The LVEF value will be picked in the following hierarchy: current hospitalization echocardiogram, current hospitalization ventriculogram/magnetic resonance, previous hospitalization echocardiogram, previous hospitalization ventriculogram/magnetic resonance.
   d) Demographics and clinical variables:
      a) Age
      b) Gender
      c) Race
      d) Insurance status
      e) Community of residence
      f) Prior hospitalization for HF
      g) Heart Rate at presentation
      h) Systolic blood pressure at presentation
      i) Diastolic blood pressure
      j) Last hemoglobin
      k) Last serum creatinine- to calculate eGFR
      l) Last BUN
      m) Arrhythmias: Atrial fibrillation/atrial flutter
      n) Coronary artery disease/h/o MI
      o) Severe valvular disease
      p) Pulmonary hypertension
      q) chronic bronchitis/COPD/asthma
      r) Diabetes mellitus
      s) smoking status
      t) Sleep apnea
      u) Stroke or TIA

   e) Treatment at discharge: ACE inhibitors or angiotensin II receptor blockers, beta blockers, diuretics, aldosterone antagonists; use of inotropes while hospitalized

Outcome of interest:
    1 year mortality and time to event

Summary of data analysis:

All analyses will be weighted to account for the sampling fractions in this community surveillance data. Chi-square analyses will be used for comparison of categorical variables and analysis of variance (ANOVA) will be used for continuous variables. Highest levels of BNP will be compared across BMI groups in HFpEF and HFrEF. Associations between BNP levels and mortality by logistic regression (in hospital mortality) and by Cox proportional hazards models (for one-year follow-up after discharge), after controlling the potential confounders such as demographics, clinical and comorbidity variables with analyses stratified by BMI. Sub-group analysis will be also be performed by presence or absence of atrial fibrillation. This analysis will be carried for HFpEF and HFrEF patients.

Of note, kidney function will be primarily evaluated by estimated GFR. The MDRD equation incorporating age, sex, race and serum creatinine will be used.

Limitations:

Information is limited to that which was documented and abstracted from the medical record. There are patients with missing data for ejection fraction, BNP and BMI. However, based on initial estimates available, we should have adequate numbers of patients for the proposed analyses. BNP levels are available for the majority of patients and a smaller proportion of patients have NT-proBNP levels. Based on final numbers in the database, if only a small group have NT proBNP, we may exclude those patients for analyses. However, if a larger proportion of patients have NT-proBNP levels, for the purposes of mortality analyses by BMI, we will consider analyses by quartiles or tertiles of BNP/NT-proBNP.

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 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)?

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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