**ARIC Manuscript Proposal # 2395**

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| **PC Reviewed: 7/8/14** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Heart Failure, Obesity Paradox and Cardiac Biomarkers

**b. Abbreviated Title (Length 26 characters)**: Obesity, Biomarkers and Heart Failure

**2. Writing Group**:
Writing group members:

Yashashwi Pokharel MD, MSCR, Wensheng Sun MPH, Wenyaw Chan PhD, Salim Virani MD, PhD, Vijay Nambi MD, PhD, Ron Hoogeveen PhD, Patricia Chang, MD, MHS, Chiadi Ndumele MD, MHS, Scott Solomon MD, Biykem Bozkurt MD, PhD, Elizabeth Selvin, PhD, Christie Ballantyne MD, Anita Deswal MD, MPH.
Others welcome

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

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**3. Timeline**: Analysis to be started as soon as possible. Manuscript to be drafted within 6 months of data analysis.

**4. Rationale**:

Obesity and overweight affects about 2/3rd of US population.[1] Obesity has been independently associated with incident heart failure (HF),[2] including in the Atherosclerosis Risk In Communities (ARIC) study.[3] Several studies,[4-6] including ours[7] have shown that obesity may be associated with a better prognosis in established HF, termed – obesity paradox – indicating that overweight/obesity may be associated with lower mortality in those with symptomatic HF. One potential explanation for this paradox is that the HF patients who are able to gain or preserve their weight may represent a non-catabolic subgroup of HF patients with different neurohormonal, inflammatory and metabolic profiles.[8] In addition, there may be marked heterogeneity in the degree of myocardial dysfunction in obese individuals who present with symptoms of shortness of breath and fluid retention and are hospitalized for HF. Using the ARIC study (MS proposal #1144: manuscript currently under revision for JACC, and presented at the AHA, 2013 [Khalid U…and **Deswal A.** Obesity Paradox in Heart Failure: Not all Cardiac Cachexia. *Circulation*. 2013;128:A15840]), we have for the first time demonstrated that individuals who were overweight [body mass index (BMI) 25 - <30 kg/m$^2$] or obese (BMI $\geq$ 30 kg/m$^2$) before the onset of HF had lower mortality after HF development, compared to those with normal BMI (18.5 - <25 kg/m$^2$), independent of comorbidities and demographic profile. Our data indicates that weight loss from advanced HF may not completely explain the protective effect of higher BMI in HF patients; pre-existing obesity prior to the development of HF was associated with better survival in HF patients.

Cardiac troponin T measured using high-sensitivity assay (hsTnT) is a very sensitive marker of subclinical myocardial injury.[9] We have shown that hsTnT predicts incident HF in the ARIC study,[10] and several other studies of community dwelling otherwise asymptomatic individuals have demonstrated similar findings.[11, 12] In addition, higher levels of hsTnT were also associated with increased cardiac and total mortality.[10-12] Furthermore, increasing levels of hsTnT over 2-3 years in the Cardiovascular Health Study increased the risk of HF and cardiovascular death.[11]

N terminal-pro B-type natriuretic peptide (NT-proBNP) is a very sensitive marker of myocardial stretch,[13] and has been associated with various cardiovascular events including HF and death.[14-16] Furthermore, fluctuations in NT-proBNP levels over time in the Cardiovascular Health Study were also associated with dynamic changes in cardiovascular risk.[17]

As noted above, we have shown for the first time that overall the presence of overweight and obesity *prior* to the onset of HF was associated with lower mortality after HF development compared to individuals with normal BMI, i.e., obesity paradox using pre-HF BMI (MS # 1144, revision pending at JACC, lead author Deswal A.). However, we believe that there is marked heterogeneity in the degree of underlying myocardial

damage/dysfunction in obese individuals who are ultimately admitted to the hospital with the constellation of symptoms and signs consistent with heart failure, including shortness of breath and fluid retention. Therefore, we postulate that the levels of cardiac biomarkers (a measure of myocardial stretch and subclinical myocardial injury) measured before the onset of HF will be helpful in stratification of overweight and obese individuals at increased and lower risk for adverse outcomes after the development of the clinical HF syndrome. Thus we may be able to use the biomarkers to identify 'healthy' obese individuals who may have HF driven mostly by non-cardiac obesity-related mechanisms vs. 'unhealthy' obese where HF is driven to a greater extent by myocardial damage/dysfunction. We believe that the obesity paradox may only be observed in "biomarker-healthy obese" individuals and not in the "biomarker-unhealthy obese", as stratified by levels of the cardiac biomarkers (hsTnT and NT-proBNP) prior to incident HF. These groups may potentially require different therapies.

The ARIC cohort, with excellent characterization of various measures of obesity at baseline and at follow-up visits, as well as serial biomarker measurements, along with the availability of long-term follow up, provides an opportunity to further investigate this issue. A very important aspect of the ARIC study as compared to other clinical data sets is the availability of hsTnT in addition to NT-pro BNP levels before incident HF.

## 5. Hypothesis/Study Questions:

Hypotheses:

1a) Overweight or obese individuals with elevated levels of cardiac biomarkers (hsTnT and NT-proBNP) prior to the development of HF will have increased total and cardiovascular mortality after the development of HF compared to overweight and obese individuals with lower levels of cardiac biomarkers.

1b) Overweight or obese individuals with elevated levels of cardiac biomarkers (hsTnT and NT-proBNP) prior to the development of HF will not demonstrate the obesity paradox, i.e. they will have similar risk for total and cardiovascular mortality after the development of HF compared to normal weight individuals.

2) Overweight and obese individuals who have an increase in levels of cardiac biomarkers (hsTnT and NT proBNP) between ARIC Visits 2 to 4 and have incident HF after Visit 4 will have increased total and cardiovascular mortality after the development of HF, compared to overweight and obese individuals who have stable levels or a reduction in hsTnT and NT-proBNP levels prior to incident HF.

## 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).

**Analyses:**

**Hypothesis 1 a)** Overweight or obese individuals with elevated levels of cardiac biomarkers (hsTnT and NT-proBNP) prior to the development of HF will have increased

total and cardiovascular mortality after the development of HF compared to overweight and obese individuals with lower levels of cardiac biomarkers.

The study cohort for this analysis will include individuals with an incident HF hospitalization 6 months or more after ARIC Visit 2. We will exclude cohort members with prevalent HF before and at ARIC Visit 2, and with missing data related to biomarkers and BMI. Standard ARIC race/center exclusions will also be applied.
The outcomes include all-cause mortality and cardiovascular mortality after the incident HF hospitalization. Similar to our prior analysis (MS# 1144), pre-morbid (preHF) BMI will be defined as the BMI measurement from a ARIC study visit that occurred 6 months or more prior to the date of incident HF (referred to as pre-HF visit). Patients with HF will be categorized by the pre-morbid BMI into normal, overweight and obese groups defined by BMI 18.5 - <25 $kg/m^2$, 25 - < 30 $kg/m^2$ and $\geq$ 30 $kg/m^2$, respectively. Patients in the underweight category (BMI < 18.5 $kg/m^2$) will be excluded because of small numbers and possible other preexisting comorbidities that may have led to a cachectic state.

Similarly cardiac biomarkers will be used from Visit 2 provided that there is at least a 6-month interval between the Visit and the incident HF hospitalization. All other covariates will be assessed at the last study Visit at least 6 months prior to the incident HF hospitalization, i.e. the pre-HF visit (or last available value), similar to our prior analysis (MS# 1144).

Proportional hazard assumption will be verified. All-cause and cardiovascular mortality will be examined after the incident HF hospitalization by BMI groups using univariable. as well as multivariable Cox proportional hazards regression models. For this analysis, our reference group will be overweight/obese individuals with lower levels of biomarkers as defined below. Follow up will be until study participants have an outcome of interest, they are lost to follow-up, or survive until December 31$^{st}$ 2011.

Similar to our model in prior analysis covariates (obtained from the preHF Visit or last available value) in multivariable models will include:

- Demographic variables: age, gender, race, education level and health insurance status
- Comorbidities: hypertension, diabetes, total cholesterol, smoking, alcohol use, prior MI, coronary heart disease, TIA/stroke and cancer
- Other prognostic factors in HF: systolic blood pressure, eGFR.

Finally we will add hsTnT and NT-proBNP to the above model in separate analysis. Similar to our prior analyses,[10, 18] we will use 4 pre-specified categories of hsTnT (<5, 6-8, 9-13 and ≥14 ng/L) and 25$^{th}$, 50$^{th}$ and 75$^{th}$ percentiles of NT-proBNP values. Because the time between the measurement of the biomarkers and the incident HF hospitalization could vary significantly between individuals in the cohort, these models will also include the variable of time between the biomarker measurement and the incident HF hospitalization.

In sensitivity analysis, we will exclude individuals with prevalent coronary heart disease and use the same models as above, except that variables such as prior MI and coronary

heart disease will not be included in the adjusted model. Analysis will also be performed by race and gender subgroups. If adequate numbers of individuals are available, subgroup analysis will be conducted for those with HF with preserved ejection fraction (HFpEF) vs. HF with reduced ejection fraction (HFrEF), for the subset of HF hospitalizations for which we can obtain left ventricular ejection fraction (LVEF) data (2005 onwards) from the ARIC HF surveillance study.

**Hypothesis 1 b)** Overweight or obese individuals with elevated levels of cardiac biomarkers (hsTnT and NT-proBNP) prior to the development of HF will have similar risk for total and cardiovascular mortality compared to normal weight individuals who develop HF.

The analysis plan for this hypothesis is similar to that for hypothesis 1 a) except that our reference group for this analysis will be normal weight individuals with lower levels of biomarkers. We will also test for interaction between BMI and biomarkers in the mortality models.

**Hypothesis 2**: Overweight and obese individuals who have an increase in levels of cardiac biomarkers (hsTnT and NT proBNP) between ARIC Visits 2 to 4 and have incident HF after Visit 4 will have increased total and cardiovascular mortality after the development of HF, compared to overweight and obese individuals who have stable levels or a reduction in hsTnT and NT-proBNP levels prior to incident HF.

This analysis will exclude individuals with prevalent HF at or before Visit 4 or those with incident HF within 6 months after Visit 4. Cox proportional hazard models similar to those used for hypothesis 1 will be developed. The difference is that we will replace the pre-HF biomarker levels with changes in hsTnT and NT-proBNP from Visits 2 to 4. We will use multiple approaches to assess changes in the biomarkers. For example, we will use absolute change (calculated as Visit 4 minus Visit 2 levels), which will be defined as increased in biomarker level if it is greater than or equal to the median of the change and defined as not increased if it is lower than the median. For values of hsTnT and NT-proBNP below the lower limits of detection, we will assign a value equal to half of the lower limits of detection.[18] For hsTnT, we will also consider other approaches such as "incident detectable" (i.e., progression from "undetectable" level [hsTnT<5 ng/L] at Visit 2 to ≥5 ng/L at Visit 4) as well as "incident elevation" (i.e., progression from <14 ng/L at Visit 2 to ≥14 ng/L at Visit 4). HsTnT level of ≥14 ng/L is approximately 90$^{th}$ percentile for the ARIC population. Consistent with the prior literature, changes in the hsTnT will also be defined as increased levels if they increase by >50% at Visit 4 compared to Visit 2; decreased if they decrease by >50% at Visit 4 compared to Visit 2; and stable if they change by ≤50% between the visits.[11] For those with undetectable levels of hsTnT at Visit 2, the reference group will be the group that also remained undetectable at Visit 4; and for those with detectable levels at Visit 2, the reference group will be the group that decreased at Visit 4 (Table). This method will allow us to compare the changes to address possible confounding by baseline hsTnT levels.

| Visit 2 | Visit 4 options/ reference group |
|---|---|
| < 5 ng/dL (undetectable) | < 5 ng/dL (reference group)<br>≥5 ng/dL |
| ≥5 ng/dL (detectable) | >50% increase<br>>50% decrease (reference group)<br>≤ 50% change |

Because the time between the measurement of the biomarkers and the HF hospitalization could vary significantly between individuals in the cohort, the time between the biomarker measurement at Visit 4 and the incident HF hospitalization will also be entered into the model.

Other covariates will be used as described for the analysis for hypothesis 1. Furthermore, since hsTnT measurements will likely be higher in patients with CHD, in a sensitivity analysis, we will exclude individuals with prevalent coronary heart disease and use the same models as above, except that variables such as prior MI and coronary heart disease will not be included in the adjusted models.

Race and gender based subgroup analysis will be performed.

Subgroup analysis will also be conducted for patients with HF with preserved ejection fraction (HFpEF) vs. HF with reduced ejection fraction (HFrEF) for the subset of HF hospitalizations for which we can obtain left ventricular ejection fraction (LVEF) data (2005 onwards) from the ARIC HF surveillance study, although it is possible that we may not have enough statistical power to examine by these sub-groups.

**Limitations:**

1. We will not have assessment of ejection fraction or of NYHA class of HF to assess severity and type of HF [HF from reduced ejection fraction (HFREF) or HF from preserved ejection fraction (HFPEF)] for all patients. However, EF measurements from hospitalizations in and after 2005 have been collected for all cohort members in the ARIC HF surveillance study and can be utilized for a subgroup analysis as detailed above. Furthermore, we will use several variables that have been shown to significantly affect outcomes of patients with HF to adjust for in the multivariable analyses. In addition, since all patients will have had a HF hospitalization, the group is somewhat more homogenous and sicker than a group that would include all outpatients with HF. A prior hospitalization for HF has been shown in multiple studies to be a major predictor of poor outcomes in patients with HF.
2. It is plausible that individuals with elevated levels of biomarkers may die before they develop HF, and therefore to account for the possibility of potential competing risk, we will perform a sensitivity analysis taking into account competing risk for non-HF mortality such as using the subdistribution relative hazard in a multivariable model.[19, 20]
3. Because patients who are sicker may die early, the eligible study participants for hypothesis 2 could represent a healthier cohort – i.e., many individuals with increasing levels of hTnT or NT-proBNP after Visit 2 may die before and may not return for Visit 4, i.e. for the second measurement. To address this, we will

consider using inverse probability of attrition weighting analyses to adjust for the healthy selection bias.

**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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?**

#1144: Deswal et al. The Obesity Paradox in Heart Failure

There is no overlap with the above proposal. Proposal # 1144 examines the prognostic role of obesity in patients that develop HF. Biomarkers were not used for that analysis.

# 2352: Ndumele et al. Weight History, Subclinical Myocardial Injury and Incident HF: The ARIC Study

This proposal examines BMI vs. waist circumference for development of subclinical myocardial injury and development of incident HF, and there is no overlap. The first author of this proposal, Dr. Ndumele, is also a coauthor in our study.
# 2142 Ndumele et al. Obesity and the Use of NT-proBNP for Heart Failure Prediction: The ARIC Study

This proposal examines the association of NT-proBNP with incident HF by different categories of BMI, and there is no overlap. The first author of this proposal, Dr. Ndumele, is also a coauthor in our study.

#2025 Ndumele et al. Obesity and Subclinical Myocardial Injury: The ARIC Study

This proposal examines the association of BMI with levels of hs-cTnT, and evaluates the extent to which this association is explained by traditional risk factors. It also assesses the prognostic implications by obesity status. Unlike this proposal, our current proposal will compare if overweight/obese individuals who develop HF and have increased hs-cTnT before HF development have increased risk of death (or CV death) after the development of HF compared to overweight/obese individuals and normal weight individuals with lower levels of hs-cTnT. The first author of Proposal # 2025, Dr. Ndumele, is also a coauthor on our study.

**11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __ X __ Yes ___ No**

**11.b. If yes, is the proposal**

**___ A. primarily the result of an ancillary study (list number* 2009.16 and 2008.10)**

**___ 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. 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.**

**References:**


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