ARIC Manuscript Proposal # 1144r

PC Reviewed: ___/___/06	**Status: _____**	**Priority: ____**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The Obesity Paradox in Heart Failure

b. Abbreviated Title (Length 26 characters): Obesity and Heart Failure Prognosis

2. Writing Group:

Writing group members: Anita Deswal, Biykem Bozkurt, Wayne Rosamond, Gerardo Heiss, Lloyd Chambless, Patricia Chang, Laura Loehr, Christie Ballantyne, Eyal Shahar, Josef Coresh

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AD__ **[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 3 months of data analysis.

4. Rationale:

Obesity-related diseases now threaten to reach epidemic proportions in the United States. Nearly 60 percent of the adult population of the United States is overweight or obese, resulting in significant morbidity and mortality.[1] Obesity is strongly associated with increased risk of developing cardiovascular diseases such as diabetes mellitus, atherosclerosis, hypertension and stroke. Although controversy previously existed with regard to whether obesity is an independent risk factor for heart failure (HF),[2,3,4] an analysis from the Framingham Heart Study, reported that increased body-mass index was indeed an independent risk factor for development of heart failure.[5]

Intuitively, one would anticipate that obesity would also adversely affect the outcome for patients with symptomatic HF. Surprisingly, studies by us and others have observed obesity to be associated with a better prognosis in HF patients; this phenomenon has been termed the "**obesity paradox**".[6,7,8] These studies have shown that in patients with symptomatic HF, obesity or overweight status may be associated with a lower risk for mortality compared with normal weight status. 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. The known protective effects of the ability to maintain or gain weight in other chronic diseases or catabolic states such as AIDS or certain malignancies lend support to this concept. Thus spontaneous weight loss (cachexia in extreme cases) after the development of HF may characterize a sicker group of patients with HF and may thus be associated with greater mortality.[9] However, it is not clear if weight loss after the development of HF gives rise to the paradoxical finding of better survival in obese HF patients or whether it is the pre-existing obesity prior to the development of HF that is truly associated with better survival in HF patients.

The ARIC cohort, with excellent characterization of various measures of obesity at baseline and at follow–up visits, some of which occur after the development of HF, and with the availability of long-term follow up, provides an opportunity for further investigating the obesity paradox in HF. The proposed study will be novel in that we will examine the prognostic implications of premorbid obesity (prior to the development of HF) in HF patients and of weight loss after development of HF in comparison to weight status prior to the development of HF.

References

1. Must A, Spadano J, Coakley EH et al. The disease burden associated with overweight and obesity. JAMA 1999;282:1523-1529.
2. Hubert HB, Feinleib M, McNamara PM et al. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation 1983;67:968-977.
3. He J, Ogden LG, Bazzano LA et al. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med 2001;161:996-1002.
4. Massie BM. Obesity and heart failure--risk factor or mechanism? N Engl J Med 2002;347:358-359.

5. Kenchaiah S, Evans JC, Levy D et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305-313.
6. Bozkurt B and Deswal A. Obesity as a prognostic factor in chronic symptomatic heart failure. Am Heart J 2005;150:1233-1239.
7. Lissin LW, Gauri AJ, Froelicher VF et al. The prognostic value of body mass index and standard exercise testing in male veterans with congestive heart failure. J Card Fail 2002;8:206-215.
8. Horwich TB, Fonarow GC, Hamilton MA et al. The relationship between obesity and mortality in patients with heart failure. J Am Coll Cardiol 2001;38:789-795.
9. Anker SD, Ponikowski P, Varney S et al. Wasting as independent risk factor for mortality in chronic heart failure. Lancet 1997;349:1050-1053.

5. Main Hypothesis/Study Questions:

Main Hypotheses:

1. Pre-existing obesity prior to the development of HF, is an independent risk factor for increased all-cause mortality and cardiovascular mortality after the development of HF.

2. Weight loss in sicker patients after the development of HF (from baseline weight prior to the development of HF) is responsible for the obesity paradox, i.e., the apparent association of obesity with better survival in HF patients.

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).

Inclusion: The study cohort will include patients with an incident HF hospitalization (defined by HF ICD-9 code: 428) at any time after enrollment into the ARIC study until the latest time that HF hospitalization data is available.
Exclusion: Cohort members with HF at enrollment, i.e. at Visit 1, based on medications used for HF (n=83) or symptoms suggestive of HF with use of digoxin or diuretics (n=517) will be excluded.
Outcomes: All-cause mortality and cardiovascular mortality.
Analyses:
For Hypothesis 1: Pre-existing obesity prior to the development of HF, is an independent risk factor for increased all-cause mortality and cardiovascular mortality after the development of HF.
All-cause and cardiovascular mortality will be examined after the incident HF hospitalization by obesity groups using univariate as well as multivariate Cox proportional hazards models. Obesity groups will be defined by obesity measures (including BMI as well as waist-hip measures) at the last available visit prior to the HF hospitalization, provided that there is at least a 6 month interval between the visit and the hospitalization.
Covariates in multivariable models will include:

- Demographic variables: age, gender, race, education status, family income and health insurance status
- Comorbidities: hypertension, diabetes, smoking, chronic lung disease, prior MI, ischemic heart disease, TIA/stroke and cancer
- Other prognostic factors in HF: systolic blood pressure, serum creatinine, hemoglobin, LVH on EKG
- Medications: ACE inhibitors and beta blockers.

Covariates will be assessed at the last study visit prior to the HF hospitalization (or last available value). The prognostic importance of obesity will also be examined by race and gender subgroups. Another analysis with fewer patients will be conducted where pre-existing obesity groups will be based on the anthropometric measures at the last visit that occurred only within a well defined 2-4 year time period prior to the HF hospitalization. We have chosen not to use obesity measures at the baseline visit (first visit) for all cohort members because this could lead to a very variable time interval among cohort members between the obesity measures and the HF hospitalization (0-16 years).

By report, till the end of 2003, there have been 1276 incident HF hospitalizations in the ARIC cohort (excluding prevalent HF at the baseline visit) and the one-year mortality after incident HF hospitalization is 21%. Furthermore, we will use all mortality data available, rather than only one-year mortality. Therefore, using a time to event analyses, we should have adequate events for the analysis.

For Hypothesis 2: Weight loss in sicker patients after the development of HF (from baseline weight prior to the development of HF) is responsible for the obesity paradox, i.e., the apparent association of obesity with better survival in HF patients.

For the subset of patients that had a study visit after the incident HF hospitalization (at least ~ 900 patients), we will examine the prognostic implications of weight loss (> 5-10% reduction in BMI and in waist-hip measures) between the last visit $\geq$ 6 months prior to and the first visit $\geq$ 6 months after the incident HF hospitalization. Univariate as well as multivariate Cox proportional hazards modeling will be used to examine all-cause mortality and cardiovascular mortality after the study visit post-HF hospitalization, the visit at which the weight loss will be assessed. Prior studies that have examined weight loss in patients with HF have found cutoffs of 6%, 7.5% and 10% to be useful as predicting outcome.[1, 2] On the basis of these studies, we have picked the range of > 5-10% weight loss reduction in BMI and other obesity measures. A priori, we would like to examine the weight loss cutoffs of 5, 7.5 and 10% to evaluate which cutoff best predicts outcomes. In addition, data on waist-hip measures will allow us to examine whether differences in peripheral or central weight loss have differential effects on survival. For this analysis, the covariates will be assessed at the study visit after HF hospitalization (or last available value). The covariates assessed will be the same as those listed for analyses 1. In addition, the use of loop diuretics, as a marker of greater severity of HF will be used for risk-adjustment.

Since the time between the HF hospitalization and the following study visit can vary, the post-hospitalization weight value would be determined at different time intervals for different patients, depending on the time of visit and hospitalization. To partly account for confounding introduced by a variable time interval at which weight loss is assessed

after hospitalization, we will attempt to use a variable defined as the duration of heart failure, i.e. the time from the incident HF hospitalization to the following ARIC study visit to try to adjust to some extent for this variability. In addition, we will perform a subgroup analysis, in which we only analyze data from patients with an ARIC study visit within 6 months to 1 year following the hospitalization to determine if the results are similar to the main analysis.

In addition, when assessing the effect of weight change on the survival from HF, we will compare the results with and without adjustment of pre-existing obesity.
Some patients may gain weight after HF hospitalization. To address the issue of weight gain, we will first perform an analysis that examines 3 groups of patients: patients with weight loss, patients with preserved weight and patients with weight gain. If outcomes appear similar in patients with preserved weight and weight gain, these patients can be grouped together for the final analysis. If differences are noted between these 2 groups, then the analysis will need to be performed with the 3 separate groups using patients with preserved weight as a reference group.

References:

(1) Anker SD, Negassa A, Coats AJ et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet 2003 March 29;361(9363):1077-83.

(2) Anker SD, Ponikowski P, Varney S et al. Wasting as independent risk factor for mortality in chronic heart failure. Lancet 1997;349:1050-3.

Limitations:
1. Although we will not have assessment of ejection fraction or of NYHA class of HF to assess severity of HF, 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 these patients have been hospitalized with HF, 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. We will not be able to differentiate spontaneous weight loss from planned weight loss. However, in practice, planned weight loss is likely infrequent in a HF population.

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)?

927: Heart Failure Incidence and Survival: 13 year follow up of the ARIC cohort.
1125: Diabetes, obesity, insulin resistance as risk factors for incident hospitalized heart failure: the ARIC study.

There is no overlap with the above proposals. Proposal # 927 examines the overall incidence of HF hospitalization, risk factors for development of HF and the one-year mortality after incident HF hospitalization. Proposal # 1125 examines the important of obesity as a risk factor for the development of HF, whereas our study proposal examines the prognostic role of obesity in patients that develop HF. In addition, some of the co-investigators on our study proposal are principal investigators for the other 2 proposals and working with then will ensure that no overlap occurs between the proposed study and the other manuscript proposals.

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. primiarly 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.**