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Myocardial Injury, Obesity, and the Obesity Paradox

The ARIC Study

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ABSTRACT

OBJECTIVES This study sought to determine whether pre-heart failure (HF) myocardial injury explains the differential mortality after HF across weight categories.

BACKGROUND Obesity is a risk factor for HF, but pre-HF obesity is associated with lower mortality after incident HF. High-sensitivity cardiac troponin T (hs-cTnT) is a sensitive marker of myocardial injury, and predicts incident HF and mortality.

METHODS Stratifying 1,279 individuals with incident HF hospitalizations by their pre-HF hs-cTnT levels ($<$ and $\geq$ 14 ng/l), we examined the association of pre-HF body mass index (BMI) with mortality after incident HF hospitalization in the ARIC (Atherosclerosis Risk In Communities) study.

RESULTS Mean age at HF was 74 years (53% women, 27% black). Individuals with pre-HF hs-cTnT $\geq$14 ng/l had higher mortality after incident HF (hazard ratio [HR]: 1.46; 95% confidence interval [CI]: 1.18 to 1.80) compared to individuals with hs-cTnT $<$14 ng/l in an adjusted model including BMI. Compared with normal weight subjects, the mortality was lower in overweight (HR: 0.69, 95% CI 0.48-0.98) and obese individuals (HR: 0.50; 95% CI: 0.35 to 0.72) with hs-cTnT $<$14 ng/l; and in those with hs-cTnT $\geq$14 ng/l (overweight HR: 0.50; 95% CI: 0.30 to 0.83; obese HR: 0.56; 95% CI: 0.34 to 0.91; interaction: $p = 0.154$ between BMI and hs-cTnT). The lower mortality risk in obese and overweight subjects remained similar when log hs-cTnT was added as a continuous variable to a multivariable model, and in sensitivity analyses after further adjusting for left ventricular hypertrophy or high-sensitivity C-reactive protein.

CONCLUSION Although greater pre-existing subclinical myocardial injury was associated with higher mortality after incident HF hospitalization, it did not explain the obesity paradox in HF, which was observed irrespective of subclinical myocardial injury. (Atherosclerosis Risk In Communities [ARIC]; NCT00005131) (J Am Coll Cardiol HF 2017;5:56–63) Published by Elsevier on behalf of the American College of Cardiology Foundation.

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Obesity and being overweight affect approximately two-thirds of the U.S. population (1). Obesity is associated with an increased risk of heart failure (HF) (2,3). Paradoxically, once HF develops, obesity is associated with better prognosis (4–7). Using the ARIC (Atherosclerosis Risk In Communities) study cohort, we previously showed that individuals who were overweight and obese (using pre-HF body mass index [BMI]) before the onset of incident HF hospitalization also had lower mortality after HF development than those with normal BMI, independent of demographics and comorbidities, including cancer, smoking, and diabetes (8). Our findings suggested that weight loss from advanced HF did not completely explain the survival benefit associated with higher BMI in HF patients. One potential explanation for this obesity paradox is that the HF patients who are able to preserve their weight may represent a noncatabolic subgroup with different neurohormonal, inflammatory, and metabolic profiles (9). However, there may also be heterogeneity in the degree of myocardial injury in obese individuals who present with the constellation of symptoms and signs such as shortness of breath and fluid retention, leading to a diagnosis of HF.

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Cardiac troponin T, measured using a high-sensitivity assay (hs-cTnT), is a sensitive marker of subclinical myocardial injury (10). We have shown that hs-cTnT levels predicted incident HF in the ARIC study (11). Other studies of community dwelling and otherwise asymptomatic individuals have also demonstrated similar findings (12,13). Furthermore, higher hs-cTnT levels were also associated with increased cardiac and all-cause mortality (11–13) and a higher degree of myocardial dysfunction (13). We postulated that hs-cTnT measurements used before incident HF would be helpful in identifying overweight and obese individuals at various levels of risk for adverse outcomes after the development of the clinical HF syndrome. Undetectable or low levels of hs-cTnT, therefore, may identify "cardiac biomarker-healthy" obese individuals with lower degree of myocardial injury in whom symptoms of HF such as shortness of breath and edema are driven mostly by noncardiac obesity-related mechanisms and who would therefore have a good prognosis contributing to the obesity paradox. In contrast, "cardiac biomarker-unhealthy" obese, in whom HF is driven to a greater extent by myocardial injury/dysfunction as indexed by hs-cTnT measurements would be expected to have a poor prognosis. We postulated that the obesity paradox would be observed in "biomarker-healthy obese" individuals but not in the "biomarker-unhealthy obese," as stratified by concentrations of hs-cTnT prior to incident HF. Accordingly, we investigated the risk of mortality associated with pre-HF BMI and hs-cTnT levels in individuals who subsequently had incident HF hospitalization in the ARIC study.

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CHD = coronary heart disease

hs-cTnT = cardiac troponin T measured using high-sensitivity assay

CV = cardiovascular

HF = heart failure

NT-proBNP = N-terminal pro-B-type natriuretic peptide

METHODS

STUDY POPULATION. The ARIC study is a prospective cohort study of 15,792 individuals enrolled from the following 4 U.S. communities: Washington County, Maryland; Jackson, Mississippi; Forsyth County, North Carolina; and suburbs of Minneapolis, Minnesota (14). The baseline evaluation (visit 1) of individuals 45 to 64 years of age took place between 1987 and 1989. Participants were subsequently examined at 3 follow-up visits at approximately 3-year intervals, and after an extended interval, a fifth study visit was recently completed between 2011 and 2013. The design, recruitment, and examination protocols for the ARIC study have been described in detail previously (14). The institutional review boards at each site approved all study protocols, and informed consent was provided by all study participants. The authors are solely responsible for the design, conduct, and analyses of the study and the drafting, editing, and preparation of the final version of the manuscript. Visit 4 (1996 to 1998), at which hs-cTnT was measured in all participants, was the baseline for the current analysis. Of 11,656 visit 4 participants, 1,279 individuals who had an incident HF hospitalization at least 6 months after visit 4, were eligible for this analysis after exclusions as detailed in **Figure 1**.

MEASUREMENT OF hs-cTnT. Details regarding the hs-cTnT measurements have been previously published (11). Briefly, hs-cTnT levels were measured in 2010, from blood samples collected during ARIC visit 4, using a high-sensitivity assay, Elecsys Troponin T (Roche Diagnostics, Basel, Switzerland) with an automated Cobas e411 analyzer (Roche). The 99th percentile value for the hs-cTnT measured in a healthy reference population (20 to 70 years of age) was 14 ng/l according to the manufacturer (Roche).

BASELINE VARIABLES. Measurements were taken in standard scrub attire and no shoes. Weight was measured using a scale that was zeroed daily and calibrated quarterly. Body mass index assessment was performed at the time of hs-cTnT measurement. Pre-HF BMI was defined as the BMI measurement from ARIC visit 4, which was at least 6 months before the date of incident HF hospitalization (8). Patients with