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Indeed, combining microRNAs that influence the ST2/IL-33 pathway, the variants of single-nucleotide polymorphisms within *IL1RL1* (the gene encoding ST2), and repeatedly measured ST2 may further clarify the role of ST2 in patients with heart failure, as suggested by Dr. Patanè. Information on genetic traits in combination with temporal changes in biomarker levels may enable individualized prognostication and, ultimately, treatment response.

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Abdominal Obesity as a Risk Predictor

Closer Than Body Mass Index But Not Close Enough

We have read with interest the study of Tsujimoto and Kajio (1), who assessed the relationship between abdominal obesity and mortality among patients with heart failure and preserved (≥45%) left ventricular ejection fraction. Several issues that could influence the interpretation of the data need to be acknowledged. Although the study by Tsujimoto and Kajio (1) included a different group of patients, the interpretation of their findings is in conflict with the results of the Spanish Heart Failure Network (2), which identified body mass index and waist circumference as independent predictors of lower total mortality. The Spanish National Registry included a larger percentage of patients in New York Heart Association functional class III or IV and only 22% of patients with left ventricular ejection fractions ≥45%, whereas both studies had similar rates of ischemic etiology. Furthermore, the impact of sex and ethnic differences cannot be fully ruled out (multinational 233-site study, with a larger percentage of female subjects than the Spanish Registry). Although statistically sound, the exploration of multiple outcome variables could increase the risk of type I error and influence the results. Indeed, the unadjusted risk of death did not differ between patients with and without abdominal obesity. In this regard, abdominal obesity was defined using thresholds with body mass index as a basis rather than the relationship between waist circumference and risk. Moreover, waist circumference thresholds in a group of patients with heart failure should probably differ, given the contribution of fluid retention. Of note, endorsing the obesity paradox, overweight and obese patients had significantly lower adjusted mortality rates than patients with normal weight, with relative risk reductions of almost 50%. Moreover, among female patients, there was no association between mortality and abdominal obesity. This could potentially be related to the significant sex-related differences in subcutaneous versus visceral fat content and to the finding that these fat depots appear to have a divergent impact on both vascular phenotype and clinical outcomes (3). Further investigations should explore whether the observed incremental risk of death among patients with abdominal obesity is related to an increased ratio of visceral to subcutaneous fat (4).

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REPLY: Abdominal Obesity as a Risk Predictor

Closer Than Body Mass Index But Not Close Enough

We appreciate the comments from Drs. Rodriguez-Granillo and Carrascosa on our recent study (1). The obesity paradox is observed in patients with heart failure. Possible explanations for this paradox include residual confounding, unintentional weight loss, unmeasured comorbidities, or selection bias (2). Puig et al. (3) recently reported that higher body mass index (BMI) and waist circumference were associated with a decreased risk of all-cause mortality in patients with heart failure. Although our study also observed an inverse relationship between BMI and mortality, several analyses showed that abdominal obesity was significantly associated with an increased risk of all-cause mortality in patients with heart failure with preserved ejection fraction (HFpEF) (1). The difference in results between the 2 studies may partially reflect the methods of the multivariable analysis. The former study used a backward stepwise method, and adjustment was made using selected variables. Additionally, the former study included patients with low BMI levels, which can include patients with undernutrition and unknown or unmeasured serious comorbidities. A sensitivity analysis excluding patients with a BMI of <18.5 kg/m^2 may be needed to confirm the results. Moreover, the former study used waist circumference and not abdominal obesity. The definition of abdominal obesity differed for men and women, and that difference could influence the results. Furthermore, the 2 studies primarily differed in their study subjects: the former study included many patients with heart failure with reduced ejection fraction (HFrEF), whereas our study included only patients with HFpEF. The pathophysiology and characteristics of patients with HFpEF and HFrEF differ significantly. In addition, unlike HFrEF, little evidence supports any specific treatment for HFpEF. Our study results (1) suggest that abdominal obesity, not BMI, may be an important risk factor for mortality in patients with HFpEF. There were no significant interactions between abdominal obesity and clinically important subgroups including sex. The inability of BMI to accurately characterize the severity of obesity may be partially associated with the obesity paradox. BMI does not distinguish between fat and lean mass, and parameters such as waist circumference and waist-to-hip ratio measure body composition more accurately than BMI. Furthermore, not peripheral fat but central fat may be a more important risk factor for mortality in patients with HFpEF because visceral fat is more strongly associated with systemic inflammation. Our findings may support the recently proposed hypothesis that the presence of a systemic proinflammatory state is associated with the pathophysiological mechanisms underlying HFpEF. Further studies are needed to assess the effects of visceral fat and fat distribution on the development of HFpEF and mortality in these patients.

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