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EDITORIAL

Weight loss for patients with obesity and heart failure

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This editorial refers to 'Surgical obesity treatment and the risk of heart failure', by S. Jamaly *et al.*, doi:10.1093/eurheartj/ehz295.

Overweight and obesity, defined by body mass index (BMI), predict incident heart failure[1] even after accounting for lifestyle factors such as diet and physical activity, and other risk factors such as blood pressure, diabetes mellitus, and lipids. Furthermore, a higher BMI in middle age, or from a self-reported weight history at age 20 or 40 years, still predicts heart failure risk.[2] However, while obesity is a well-established risk for heart failure, the potential for weight loss to either prevent or treat the condition in people with obesity remains under-researched.[3] Concerns about the potential benefit from intentional weight loss exist, largely driven by a so-called obesity (or more accurately BMI) paradox, that suggests that a modest degree of overweight might be protective against mortality in those with established heart failure. Many consider the BMI paradox to result from flawed analyses that fail to account fully for reverse causality (i.e. weight is lower due to illness rather than the other way around) and collider bias (the unnecessary stratification of comparisons by a factor which is a causal result of both the exposure and outcome of interest).[4] Worries that weight loss might worsen the condition have led to guidelines recommending against weight loss in people with heart failure and only modest degrees of overweight or obesity, and only for 'symptomatic relief' in those with greater degrees of obesity.[5] More recently, a consensus statement from the Heart Failure Society of America has been more enthusiastic about the potential for treatments for weight loss including diet, antiobesity pharmacotherapy, and bariatric surgery.[6]

The findings from the Swedish Obese Subjects (SOS) cohort study (surely a gift from a study that keeps on giving) reported in this issue of the *European Heart Journal* provide further compelling evidence that weight loss (achieved after bariatric surgery) reduces the risk of people with obesity developing heart failure.[7] The SOS recruited 2010 people with obesity (BMI in men ≥34 kg/m^2 and in women ≥38 kg/m^2) for weight loss surgery and matched them to 2037 who received the then standard of medical care (losing little or no weight). SOS has already reported, with 15- to 20-year follow-up or more, that the surgical cohort had lower mortality rates of myocardial infarction, atrial fibrillation, stroke, cancer in women, and incident diabetes with increased diabetes remission.[8]

In the current study, incident heart failure was determined from a diagnosis in Swedish registries that cover 99% of the population and which have previously been shown to have a validity of 95%.[9] Fourteen subjects with a diagnosis prior to surgery were excluded. In the surgical group, BMI fell by 25% after 1 year, 18% after 6 years, and 16% at 20 years (from a baseline of 42.4 kg/m^2), while the control group's BMI was unchanged, giving a between-group difference of −8.3 kg/m^2. There was a 35% lower risk of being diagnosed with heart failure in patients treated with bariatric surgery (188 cases) compared with the control group (266 cases). Adjusting for baseline conditions, the incidence rates were 4.8 and 7.2 per 1000 patient-years, respectively, each with narrow confidence limits. Admissions for heart failure and self-reported use of heart failure medications were also lower after surgery. These risks decreased across quartiles of weight loss, although the authors recommend caution in interpreting these findings due to collinearity of weight loss and surgery; it is not possible to be sure if it was the weight loss or some other 'off target' effect of surgery that drove the benefit.

The links between obesity and heart failure are multifactorial, and have become increasingly complex with the recognition that heart failure with preserved ejection fraction (HFpEF) accounts for more than half of all those with heart failure, and that >80% of those with HFpEF are either overweight or obese.[9] HFpEF has a distinct pathophysiology compared with heart failure with reduced ejection fraction (HFrEF), with differing abnormal haemodynamics, alterations in natriuretic hormones, and cardiac remodelling, driven in part by chronic, low-grade, systemic inflammation driven by adipocytokines secreted from the expanded (visceral) adipose tissue.[10] Weight loss reverses many of these risk factors as well as modifying the abnormalities of gut microbiota (gene richness, composition, and function) that have been linked to cardiovascular pathology.[11] A recent systematic review of four randomized trials of weight loss in patients with

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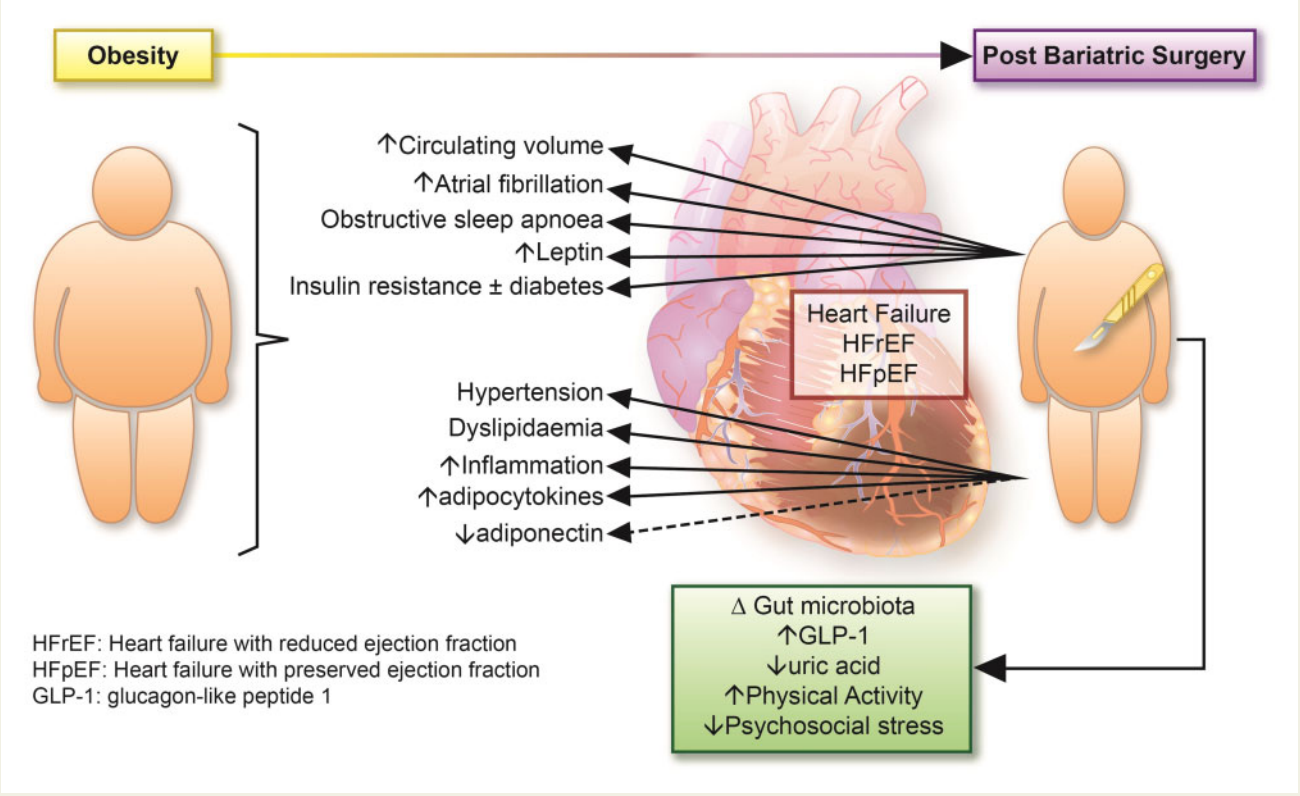

Take home figure Summary of the impact of bariatric surgery (and accompanying weight loss) on improving or reversing risk factors associating obesity with heart failure. Solid lines represent a reduction, dotted lines an increase in the biomarker. The green box lists more speculative effects of surgery that could reduce the risk of developing heart failure.

obesity and heart failure concluded that weight loss was achievable and beneficial.[12] A pilot study using protein-rich but very low-energy diets providing 800–1000 kcal/day found short-term improvements in 6-min walking test and $VO2_{max}$.[13]

Previous data from Swedish registries of nearly 40 000 obese people without previous heart failure found that gastric bypass surgery was associated with approximately one half the incidence of heart failure compared with intensive lifestyle treatment, including low- and very low-calorie diets, associations mediated by weight loss, partly mediated by the effects of treatment of interim atrial fibrillation, diabetes mellitus, and hypertension, but probably not from treatment of myocardial infarction.[14]

Are there limitations in the SOS study? This was not a randomized study—as the authors point out, ethical review at the time did not allow it—but the baseline characteristics of the intervention and control groups differed. The impact of the degree of weight reduction was analysed after pooling the intervention and control groups, and in secondary analyses, adjusted for surgical intervention and baseline BMI, only the highest quartile showed statistically significant mortality reduction. There is no echocardiographic detail, and therefore no distinction between HFpEF and HFrEF, or even for that matter classification of the severity of heart failure by New York Heart Association criteria. Registry data also clearly provide less precise information than that obtained from outcome trials where events are independently adjudicated. While weight reduction drove the benefit, the study is unable to determine which of the mediating factors associated with obesity contributed most. Another issue is that two of the forms of surgery used in the SOS study (banding and vertical banded gastroplasty) are rarely used now, and gastric bypass (GBP; the most efficacious and considered the 'gold standard') accounted for only 13% of the surgical cohort. There is no subgroup analysis by type of surgery, and this may be of importance since GBP produces profound and distinct changes in gut hormone responses to food.[15]

Despite the positive findings, bariatric surgery cannot provide an answer to the estimated 650 million individuals with overweight and obesity globally. These findings do support the need for further research into the optimal ways of preventing heart failure(s) in obesity, as well as whether nutritional, physical activity, or pharmacological approaches to reduce inflammation could, perhaps even with lower amounts of weight loss, achieve similar or even greater benefit. Similarly, evidence on how best to treat obesity in patients with established heart failure is needed. While several anti-obesity medications are now licensed, and were required to demonstrate cardiovascular safety in outcome trials, heart failure was not a required endpoint nor a standard component of the three-point MACE (major adverse cardiovascular events) outcome and was often an exclusion criterion for patient selection. The SOS results, however, add to the growing evidence that weight loss and weight loss maintenance can be achieved and need to be more widely offered to reduce the morbidty of untreated obesity.

Conflict of interest: N.F. is an employee of Novo Nordisk A.S.

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