HHS Public Access

Author manuscript

Eur J Heart Fail. Author manuscript; available in PMC 2024 January 04.

Published in final edited form as:

Eur J Heart Fail. 2023 January ; 25(1): 128–130. doi:10.1002/ejhf.2753.

Weighing in on weight loss in heart failure with reduced ejection fraction

Salvatore Carbone[1,2], **Adrian daSilva-deAbreu**[3], **Carl J. Lavie**[4,*]

[1]Department of Kinesiology & Health Sciences, College of Humanities & Sciences, Virginia Commonwealth University, Richmond, Virginia, USA

[2]Division of Cardiology, Pauley Heart Center, Department of Internal Medicine, Virginia Commonwealth University, Richmond, Virginia, USA

[3]Department of Cardiovascular Medicine, Mayo Clinic, Rochester Minnesota, USA

[4]Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School-The University of Queensland School of Medicine, New Orleans, Louisiana, USA

Energy restriction-induced weight loss to prevent cardiovascular diseases: a common prescription with limited evidence

Weight loss achieved through energy restrictions (ER) is typically recommended as a tool to improve cardiometabolic risk factors in the general population that presents with states associated with excess adiposity that may impair health, such as overweight and obesity. Despite the common thought that weight loss is beneficial in this population, the long-term benefits of weight loss on cardiovascular disease (CVD) endpoints remain uncertain, and in fact, based on limited evidence. In the Look AHEAD trial, ER-induced weight loss did not reduce the risk for CVD in patients with type 2 diabetes mellitus (T2DM), despite small, yet statistically significant, improvements in cardiometabolic risk factors. A post-hoc analysis of this study, however, suggested that 10% weight loss or more achieved within the first year of intensive lifestyle intervention was associated with a significant reduction in CVD[1]; however, because the primary pre-specified endpoints of the study were not met in the Look AHEAD trial, those potential benefits achieved with a greater weight loss within the first year should be considered exploratory in nature and, in fact, interpreted with caution.

Obesity paradox and weight loss in heart failure

Obesity remains a leading risk factor for the development of heart failure (HF), more so for HF with preserved ejection fraction (HFpEF) than HF with reduced ejection fraction

*Corresponding author. John Ochsner Heart and Vascular Institute, Ochsner Clinical School - The University of Queensland School of Medicine, 1514 Jefferson Highway, New Orleans, LA 70121-2483, USA. Tel: +1 504 842-1281, Fax: +1 504 842-5875, clavie@ochsner.org.

Conflict of interest: S.C. is supported by a Career Development Award 19CDA34660318 from the American Heart Association and by a Clinical and Translational Science Award UL1TR002649 from the National Institutes of Health to Virginia Commonwealth University. C.J.L has served as a consultant and promotional speaker for AstraZeneca for Farxiga in the US. A.d.d.A. has nothing to disclose.

(HFrEF). However, little is known about the ability of ER to prevent HF in those with overweight or obesity. Moreover, when HF is diagnosed, obesity has been consistently associated with more favourable short- and mid-term survival (i.e. obesity paradox), despite a greater risk for hospitalizations.[2] In addition to the obesity paradox, the benefits of ER-induced weight loss in HF have not been established despite being commonly prescribed in clinical practice. In fact, weight loss has been consistently associated with worse survival in patients with HF in observational studies. This is further emphasized by the fact that clinical HF guidelines do not advocate for weight loss in this population, unless patients have concomitant class II obesity (body mass index [BMI] ≥35 kg/m^2), for which short-term ER-induced weight loss studies have been associated with improved cardiorespiratory fitness (CRF) and quality of life (QoL),[3] making the prescription of ER-induced weight loss a reasonable approach in this population.

Baseline body mass index and weight loss in HFrEF: insights from EMPEROR-Reduced

In the current issue of the Journal, Anker and colleagues investigated the effects of baseline BMI and weight loss experienced during the trial on clinical outcomes and QoL in patients with HFrEF and treated with daily sodium–glucose cotransporter 2 (SGLT2) inhibitor empagliflozin 10 mg or placebo.[4] First, they found that baseline BMI did not present a significant interaction for the beneficial effects of empagliflozin on the primary composite outcome of CVD death and hospitalization for worsening HF, as well as total hospitalizations and rate of estimated glomerular filtration rate decline, further supporting the benefits of SGLT2 inhibitors in HFrEF across BMI categories. The only interaction was found for first hospitalization for HF, in which patients with BMI between 20 and 30 kg/m^2 presented the greatest benefits of empagliflozin, while the benefits appeared attenuated in patients with classes I and II obesity for this specific secondary outcome. When they investigated BMI as a continuous variable, they found that patients with BMI <25 kg/m^2 presented a greater risk of all-cause mortality, and they identified BMI between 25 and 29.9 kg/m^2 as the category associated with the lowest mortality risk, even after adjusting for common clinical prognosticators in HF, such as N-terminal pro B-type natriuretic peptide.

They further analysed the effects of empagliflozin on weight loss and found that 17.4% of participants lost more than 5% of body weight compared to 12.8% in the placebo group at 1 year. The investigators also described that greater weight loss was associated with a greater mortality rate, independent of whether they were randomized to the treatment intervention or control. As mentioned above, however, the benefits of empagliflozin persisted despite the weight loss, although the authors confirmed the previously reported obesity paradox and the potential detrimental effects of weight loss in this population. These results are consistent with a prior analysis published in the Journal, this time using dapagliflozin, in which patients with HFrEF experienced significant benefits when they were treated with dapagliflozin, despite the presence of an obesity paradox in the overall investigated population.[5] Taken together these data confirm the class-effect benefits of SGLT2 inhibitors in patients with HF, which has been recently highlighted by the clinical guidelines for HF that advocate for the early implementation of these agents in HFrEF, which can be

initiated safely and effectively even in hospitalized patients. Patients with HFrEF present a significantly reduced QoL, and when the investigators analysed the effects of empagliflozin on QoL, they found that the treatment was associated with a greater improvement in QoL assessed using the Kansas City Cardiomyopathy Questionnaire compared to placebo, without a significant interaction across BMI categories.

Finally, with regard to safety, the investigators also found that empagliflozin was safe across different BMI and weight loss categories, with a greater number of patients experiencing adverse events leading to discontinuation of therapy in those with BMI <20 kg/m^2, and a greater number of genital infections in patients treated with empagliflozin compared to placebo across different BMI categories. Of note, these effects are consistent with the previously reported safety profile of SGLT2 inhibitors.

Despite the fact that the authors suggest that empagliflozin-induced weight loss might be the result of glycosuria-induced energy deficit characteristic of SGLT2 inhibitors, we cannot differentiate with certainty whether weight loss achieved was intentional or not, which is a major limitation considering that unintentional weight loss in HF might be the result of an active catabolic state characteristic of a more severe disease state. Also, the analysis does not allow to determine the quality of weight lost by the individuals, in fact, whether weight loss resulted from a greater proportion of fat mass, lean mass, or body water is unknown. Similarly, although groups were stratified using BMI, because body composition was not analysed, it limited the generalizability of the findings to all races and ethnicities. Specifically, Asian people have a greater amount of fat mass at lower BMI categories than White individuals as well as worse metabolic outcomes, such as an elevated risk for T2DM.[6] Patients with higher BMI were also more likely to be White as well as receiving the pillars of guideline-directed medical therapy in HFrEF, which could potentially explain why the patients with higher BMI presented more favourable outcomes overall.

In addition to the lack of body composition assessment, the study did not measure important confounders with prognostic implications in HF as well as in coronary heart disease, such as CRF, physical activity (PA), and sedentary behaviours (SB). Of note, the benefits of greater CRF and/or PA and lower SB appear to be independent of weight loss,[7–12] and SGLT2 inhibitors have been shown to improve CRF in this population.[13,14]

A critical question remains on the mechanisms of action through which SGLT2 inhibitors may improve clinical outcomes and QoL in patients with HF. In addition to the improvements in CRF, typically defined as improved peak oxygen consumption, we and others have hypothesized other potential mechanisms of SGLT2 inhibitors. Pre-clinical studies have also suggested that SGLT2 inhibitors can improve the composition of fatty acid infiltration within the skeletal muscle (i.e. intramuscular fat), by increasing the amount of oleic acid, a monounsaturated fatty acid, while reducing its content of palmitic acid, a saturated fatty acid,[15] an improvement which might explain some of the increase in CRF reported after treatment with SGLT2 inhibitors. Finally, SGLT2 inhibitors may improve volume status without the activation of the renin–angiotensin–aldosterone system, and they may also improve fuel utilization by promoting the oxidation of fatty acids compared to carbohydrates in a fasting state (i.e. improved metabolic flexibility).[5]

In conclusion, Anker and colleagues are congratulated for providing additional evidence on the beneficial effects of SGLT2 inhibitors across different BMI categories and providing novel evidence that their effects may be independent of the degree of weight loss achieved with these agents in HFrEF. Future randomized controlled trials specifically designed to investigate the effects of weight loss on clinical outcomes in patients with HFrEF with ER, but also with novel weight loss pharmacotherapy as well as bariatric surgery to achieve a greater weight loss than ER alone, are urgently needed to ultimately determine if this strategy is safe and effective on improving long-term clinical outcomes in this population and more so in HFpEF.

References

1. Look AHEAD Research Group, Gregg E, Jakicic J, Blackburn G, Bloomquist P, Bray GA, et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol. 2016;4:913–21. [PubMed: 27595918]
2. Carbone S, Lavie CJ. Disparate effects of obesity on survival and hospitalizations in heart failure with preserved ejection fraction. Int J Obes (Lond). 2020;44:1543–5. [PubMed: 32313066]
3. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA. 2016;315:36–46. [PubMed: 26746456]
4. Anker SD, Khan MS, Butler J, Ofstad AP, Peil B, Pfarr E, et al. Weight change and clinical outcomes in heart failure with reduced ejection fraction: insights from EMPEROR-Reduced. Eur J Heart Fail. 2023;25:117–27. [PubMed: 36325584]
5. Carbone S, daSilva-deAbreu A, Lavie CJ. The sodium-glucose co-transporter 2 inhibitor dapagliflozin improves prognosis in systolic heart failure independent of the obesity paradox. Eur J Heart Fail. 2021;23:1673–6. [PubMed: 34427026]
6. Caleyachetty R, Barber TM, Mohammed NI, Cappuccio FP, Hardy R, Mathur R, et al. Ethnicity-specific BMI cutoffs for obesity based on type 2 diabetes risk in England: a population-based cohort study. Lancet Diabetes Endocrinol. 2021;9: 419–26. [PubMed: 33989535]
7. Lavie CJ, Laddu D, Arena R, Ortega FB, Alpert MA, Kushner RF. Healthy weight and obesity prevention: JACC health promotion series. J Am Coll Cardiol. 2018;72:1506–31. [PubMed: 30236314]
8. Kim Y, Canada JM, Kenyon J, Billingsley HE, Arena R, Lavie CJ, et al. Effects of replacing sedentary time with physical activity on mortality among patients with heart failure: National Health and Nutrition Examination Survey follow-up study. Mayo Clin Proc. 2022;97:1897–903. [PubMed: 35753825]
9. Carbone S, Kim Y, Kachur S, Billingsley H, Kenyon J, de Schutter A, et al. Peak oxygen consumption achieved at the end of cardiac rehabilitation predicts long-term survival in patients with coronary heart disease. Eur Heart J Qual Care Clin Outcomes. 2022;8:361–7. [PubMed: 33895797]
10. Carbone S, Lavie CJ, Elagizi A, Arena R, Ventura HO. The impact of obesity in heart failure. Heart Fail Clin. 2020;16:71–80. [PubMed: 31735317]
11. Elagizi A, Carbone S, Lavie CJ, Mehra MR, Ventura HO. Implications of obesity across the heart failure continuum. Prog Cardiovasc Dis. 2020;63:561–9. [PubMed: 33002458]
12. Tutor A, Lavie CJ, Kachur S, Dinshaw H, Milani RV. Impact of cardiorespiratory fitness on outcomes in cardiac rehabilitation. Prog Cardiovasc Dis. 2022;70:2–7. [PubMed: 34780726]
13. Carbone S, Billingsley HE, Canada JM, Bressi E, Rotelli B, Kadariya D, et al. The effects of canagliflozin compared to sitagliptin on cardiorespiratory fitness in type 2 diabetes mellitus

and heart failure with reduced ejection fraction: the CANA-HF study. Diabetes Metab Res Rev. 2020;36:e3335. [PubMed: 32415802]

14. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, Garcia-Ropero A, Mancini D, Pinney S, et al. Randomized trial of empagliflozin in nondiabetic patients with heart failure and reduced ejection fraction. J Am Coll Cardiol. 2021;77:243–55. [PubMed: 33197559]
15. Bamba R, Okamura T, Hashimoto Y, Majima S, Senmaru T, Ushigome E, et al. Extracellular lipidome change by an SGLT2 inhibitor, luseogliflozin, contributes to prevent skeletal muscle atrophy in db/db mice. J Cachexia Sarcopenia Muscle. 2022;13:574–88. [PubMed: 34854254]