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Sodium-glucose cotransporter 2 inhibitors in obese patients with heart failure

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While obesity increases the risk of heart failure (HF), the prognosis of obese HF patients is better than that of non-obese HF patients. This phenomenon is called the "obesity paradox" [1]. This may explain why pharmacotherapy of various HF conditions may differ in obese than to non-obese HF patients. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors have been shown to improve the prognosis of HF patients regardless of left ventricular contractility; SGLT-2 inhibitors are pivotal agents that have created a new paradigm shift in the pharmacological treatment of HF. Four large randomized controlled trials (RCTs) have been conducted to date, and in a sub-analysis of body mass index (BMI), there is a slight difference in the prognostic improvement effect of SGLT-2 [2–5]. It is hypothesized herein, that there might be a difference in the efficacy of SGLT-2 according to high and low BMI. To test this hypothesis, a meta-analysis of four large RCTs was performed. Four large RCTs (> 1000 patients) were analyzed with data from sub-analyses stratified by BMI (< 30 kg/m^2 or > 30 kg/m^2) [2–5]. Obesity was defined as BMI ≥ 30 kg/m^2. A total of 20.717 HF patients were analyzed, including 8.318 (40%) obese patients; 2 RCT used empagliflozin [2, 4], and other 2 RCT used dapagliflozin [3, 5]. Hazard ratio (HR) for primary end-point (cardiovascular death or hospitalization for HF) was pooled using the random-model generic inverse variance method after logarithm conversion (RevMan ver 5.4. Cochrane Collaboration, London, UK). Figure 1 demonstrates the results of a pooled meta-analysis. Treatment with SGLT-2 inhibitors resulted in a significant reduction in the primary end-point both in HF patients without obesity (HR: 0.78, 95% confidence interval [CI]: 0.70–0.88, $p < 0.001$, $I^2 = 32\%$, p for heterogeneity = 0.22), and HF patients with obesity (HR: 0.78, 95% CI: 0.73–0.83, $p < 0.001$, $I^2 = 4\%$, p for heterogeneity = 0.41). The effect of the SGLT-2 inhibitor was similar between HF patients with obesity and those without (p = 0.42) (Fig. 1).

The precise pathophysiology of the "obesity paradox" remains unclear. Possible mechanisms are the cardioprotective effect of various cytokines and neuroendocrine profiles, increased muscle mass and strength, higher blood pressure leading to more cardiac medications, and other factors [1]. Although the mechanism is not well-understood, epidemiological studies demonstrated that survival rates were better in obese HF patients than in low-weight HF patients. Therefore, confirmation of the effect of SGLT-2 inhibitor both for obese and non-obese HF patients might be clinically meaningful. In addition, two large-scale RCTs were included using empagliflozin in the meta-analysis and demonstrated that the effect did not vary according to BMI, similar to dapagliflozin. The present data will contribute to considering the indication of SGLT-2 inhibitor for HF patients with obesity.

However, it must be recognized that there are several caveats in the interpretation of the results of this meta-analysis. The integration of data from two different SGLT-2 inhibitors, i.e., to conclude that there is a class effect of SGLT-2 inhibitors in obese patients, further meta-analysis using different SGLT-2 inhibitors or comparing dapagliflozin and empagliflozin trials would be needed to conclude that there is

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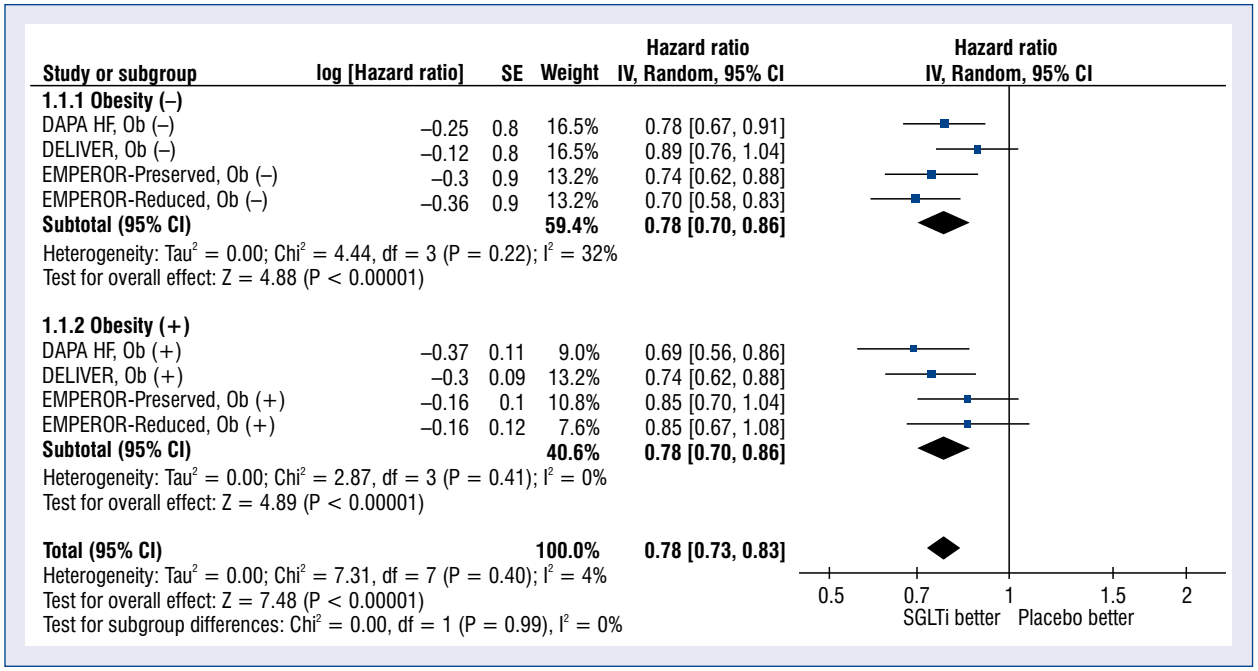

Figure 1. The hazard ratio of composite cardiac events stratified by the presence or absence of obesity; CI — confidence interval; SE — standard error; SGLTi — sodium-glucose co-transporter-inhibitor.

a class effect of SGLT-2 inhibitors in obese patients. The results of the current study only mention the potential of SGLT-2 as a whole to improve the prognosis of HF patients regardless of BMI value. Understanding these limitations, we should continue to monitor new evidence on SGLT-2 inhibitors.

Conflict of interest: None declared

References

1. Lavie CJ, Alpert MA, Arena R, et al. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. JACC Heart Fail. 2013; 1(2): 93–102, doi: 10.1016/j.jchf.2013.01.006, indexed in Pubmed: 24621833.
2. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021; 385(16): 1451–1461, doi: 10.1056/NEJMoa2107038, indexed in Pubmed: 34449189.
3. McMurray JJV, Salomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019; 381(21): 1995–2008, doi: 10.1056/NEJMoa1911303, indexed in Pubmed: 31535829.
4. Packer M, Anker S, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020; 383(15): 1413–1424, doi: 10.1056/nejmoa2022190.
5. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with preserved ejection fraction. N Engl J Med. 2023; 388(3): 286–288, doi: 10.1056/nejmc2213974.