

SHORT COMMUNICATION

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Role for GLP-1 Agonists in Patients with Obesity and Heart Failure with Preserved Ejection Fraction

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Obesity is a well-known risk factor for heart failure with preserved ejection fraction (HFpEF). Through recent clinical trials, glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists have been shown to decrease mortality and improve symptoms in patients with obesity and HFpEF. Based on the new existing data, we suggest a change in clinical practice for physicians globally. Evidence now supports the initiation of GLP-1/GIP agonists in patients with obesity and HFpEF. This short communication reviews some of the most recent data on GLP-1/GIP agonists that support their clinical indications for patients with obesity and heart failure.

Keywords: Heart failure with preserved ejection fraction; Obesity; Glucagon-like peptide-1 receptor agonists; Systemic inflammation; Glucose-dependent insulinotropic polypeptide

The Obesity is a known risk factor for heart failure with preserved ejection fraction (HFpEF) (1). Many of these patients eventually develop overt cardiac dysfunction due to visceral adiposity that induces a systemic inflammation state, which may be transduced onto the myocardium via a proinflammatory transition of epicardial adipose tissue (1,2). This creates circulatory volume expansion and pressure overload, leading to cardiovascular-kidney end-organ damage (1-3). Tirzepatide, a dual agonist of the glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors, has been shown to

have significant cardiovascular benefits in the most recent SUMMIT trial published by the New England Journal of Medicine (4). In this international, double-blinded, randomized, placebo-controlled trial, 731 patients with HFpEF and obesity (defined by a body mass index (BMI) of at least 30) received tirzepatide (up to 15 mg subcutaneously once weekly) or placebo for at least 52 weeks. Groups were assigned in a 1:1 ratio.

The two primary endpoints were death from cardiovascular causes or worsening heart failure events and the change from baseline to 52 weeks in the Kansas City Cardiomyopathy

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Questionnaire clinical summary score (KCCQ-CSS; score ranges from 0 to 100, with high scores indicating a better quality of life). Results showed that adjudicated death from cardiovascular causes or a worsening heart failure event occurred in 56 patients in the placebo (hazard ratio, 0.62; 95% confidence interval, 0.41 – 0.95; $p=0.026$) and 36 patients (9.9 %) in the tirzepatide group. At 52 weeks, the mean ($\pm$ SD) change in the KCCQ-CSS was 19.5 ± 1.2 in the treatment group compared to 12.7 ± 1.3 in the placebo group. The study ultimately concluded that tirzepatide lowered the risk of death from cardiovascular causes or worsening heart failure events compared to placebo and improved health status in patients with HFpEF and obesity.

Two other trials have been conducted, both of which evaluated the use of semaglutide (a GLP-1 agonist) in patients with HFpEF and obesity. In the STEP-HFpEF clinical trial, 529 patients with HFpEF and obesity (defined by a BMI of 30 or higher) were randomly assigned to receive once-weekly semaglutide (2.4 mg) or placebo for 52 weeks (5). The two primary endpoints were the change in body weight and the change from baseline in the KCCQ-CSS. The study demonstrated that treatment with semaglutide resulted in more substantial reductions in symptoms and limitations, greater improvements in exercise function, and greater weight loss compared to the placebo. Likewise, in the STEP-HFpEF diabetes mellitus trial, among patients with obesity, HFpEF, and type 2 diabetes, semaglutide resulted in larger reductions in physical limitations and heart failure-related symptoms, as well as greater weight loss, compared to placebo at 1 year (6).

These clinical studies ultimately show that there lies a role for GLP-1 agonists in heart failure patients with obesity. Although the exact mechanisms by which tirzepatide and semaglutide reduce mortality in obese patients with heart failure are unknown, it is proposed

that their effects are probably related to their ability to reduce fat mass, which in turn limits. The resulting expansion of plasma volume and inflammatory response that facilitates the pathogenesis of HFpEF (7-10). Among practicing clinicians, we suggest considering the prescription of a GLP-1 agonist in patients with documented HFpEF and obesity, given the potential for symptom improvement and mortality benefit. A significant limitation of these trials was the BMI criteria (a BMI of at least 30 was specified as an eligibility criterion). As such, further studies are needed to assess the role of GLP-1/GIP agonists in patients with BMIs of less than 30.

Conflict of Interest

The authors declare no relevant conflicts of interest for this article. None of the authors received any financial grant that could be considered a potential conflict of interest regarding this manuscript or its submission.

Author Contributions

English K., wrote the original draft, contributed to conceptualization, writing, reviewing, and editing. Uwibambe C., reviewed and edited the article. All authors read and approved the final version of the manuscript.

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