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FREE PREVIEW

# Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

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## Abstract

**BACKGROUND** Heart failure with preserved ejection fraction is increasing in prevalence and is associated with a high symptom burden and functional impairment, especially in persons with obesity. No therapies have been approved to target obesity-related heart failure with preserved ejection fraction.

**METHODS** We randomly assigned 529 patients who had heart failure with preserved ejection fraction and a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or higher to receive once-weekly semaglutide (2.4 mg) or placebo for 52 weeks. The dual primary end points were the change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-

CSS; scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations) and the change in body weight. Confirmatory secondary end points included the change in the 6-minute walk distance; a hierarchical composite end point that included death, heart failure events, and differences in the change in the KCCQ-CSS and 6-minute walk distance; and the change in the C-reactive protein (CRP) level.

**RESULTS** The mean change in the KCCQ-CSS was 16.6 points with semaglutide and 8.7 points with placebo (estimated difference, 7.8 points; 95% confidence interval [CI], 4.8 to 10.9; P<0.001), and the mean percentage change in body weight was −13.3% with semaglutide and −2.6% with placebo (estimated difference, −10.7 percentage points; 95% CI, −11.9 to −9.4; P<0.001). The mean change in the 6-minute walk distance was 21.5 m with semaglutide and 1.2 m with placebo (estimated difference, 20.3 m; 95% CI, 8.6 to 32.1; P<0.001). In the analysis of the hierarchical composite end point, semaglutide produced more wins than placebo (win ratio, 1.72; 95% CI, 1.37 to 2.15; P<0.001). The mean percentage change in the CRP level was −43.5% with semaglutide and −7.3% with placebo (estimated treatment ratio, 0.61; 95% CI, 0.51 to 0.72; P<0.001). Serious adverse events were reported in 35 participants (13.3%) in the semaglutide group and 71 (26.7%) in the placebo group.

**CONCLUSIONS** In patients with heart failure with preserved ejection fraction and obesity, treatment with semaglutide (2.4 mg) led to larger reductions in symptoms and physical limitations, greater improvements in exercise function, and greater weight loss than placebo. (Funded by Novo Nordisk; STEP-HFpEF ClinicalTrials.gov number, NCT04788511.)

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A list of the STEP HFpEF trial committees and investigators is provided in the Supplementary Appendix, available at NEJM.org.