



# Efficacy and Safety of Semaglutide for the Management of Obese Patients With Type 2 Diabetes and Chronic Heart Failure in Real-World Clinical Practice

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**Background:** The impact of glucagon-like peptide-1 receptor agonists on patients with heart failure has not been fully described. Our main objective was to evaluate the safety and clinical and glycemic efficacy of once-weekly semaglutide in obese patients with type 2 diabetes and heart failure.

**Methods:** In this observational, retrospective, real-world study, we enrolled outpatients with type 2 diabetes, obesity, and heart failure who started semaglutide and were followed-up on at 3, 6, and 12 months.

**Results:** A total of 136 patients were included. From baseline to 12 months, there was a significant improvement on the Kansas City Cardiomyopathy Questionnaire total symptom score ( $59.0 \pm 24.1$  vs  $79.9 \pm 28.4$  points,  $p < 0.01$ ), a reduction in the proportion of patients with New York Heart Association functional class III (40.4% to 16.2%,  $p < 0.01$ ), and a reduction in N-terminal pro-brain natriuretic peptide levels ( $969.5 \pm 653.5$  vs  $577.4 \pm 322.1$  pg/mL,  $p < 0.01$ ). Emergency department visits due to heart failure, hospitalizations due to heart failure, and all-cause hospitalizations also declined. Additionally, significant reductions in glycated hemoglobin (-1.4%) and body weight (-12.7 kilograms) were observed as well as a de-intensification of antidiabetic therapy. Moreover, semaglutide was safe and well-tolerated.

**Conclusion:** In obese patients with type 2 diabetes and heart failure, the use of once-weekly semaglutide was safe and clinically efficacious, improving health and functional status. Nevertheless, more strong evidence on glucagon-like peptide-1 receptor agonists in heart failure is required.

**Keywords:** obesity, type 2 diabetes, heart failure, semaglutide, health status

## INTRODUCTION

In recent years, heart failure (HF) has become the most common cardiovascular disease in patients with type 2 diabetes (T2D); its incidence is 2.5 times greater than acute coronary disease (1). In addition, HF is among the most common causes of hospital admissions (2) and hospitalization rates for this disease are exponentially higher than for coronary artery disease and stroke (3). Patients with concomitant HF and T2D have a lower quality of life, worse symptoms and higher mortality compared to patients without T2D (4).

The mail clinical guidelines published by scientific societies in Europe, the United States of America, and Canada have made important changes to recommendations on the choice of treatment and management approach for patients with T2D. They recommend the preferential use of glucagon-like peptide-1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT-2) inhibitors that have proven renal and cardiovascular benefits for patients with established cardiovascular disease or those at high risk for cardiovascular disease if there are no contraindications for their use (5–8).

Safety concerns, comorbidities, or their healthcare environment may affect many patients' selection of glucose-lowering drugs (5). Most patients require intensification of glucose-lowering drugs. For those with T2D and HF -especially HF with reduced ejection fraction- or those who are at high risk of developing HF, chronic kidney disease, evident atherosclerotic cardiovascular disease, or any combination of these diseases, the use of SGLT-2 inhibitors with demonstrated cardiovascular benefit as an add-on metformin is recommended. However, GLP-1 receptor agonists with proven cardiovascular benefits have been recommended as the treatment of choice for patients with established atherosclerotic cardiovascular disease or patients who are at very high risk for developing it. Given the higher degree weight loss that has generally been reported with GLP-1 receptor agonists, their use is recommended for patients who are prioritizing weight loss or weight maintenance (5–8). In regards to HF outcomes, GLP-1 receptor agonists have not been associated with significant improvements in pivotal cardiovascular outcomes clinical trials (9–16). Nevertheless, when patients in all GLP-1 receptor agonists' trials were analysed in a meta-analysis conducted by Kristensen et al. (17), use of GLP-1 receptor agonists was associated with a significant reduction in HF hospitalizations.

Despite this evidence, the impact of GLP-1 receptor agonists in patients with HF has not been fully described in the literature. In this study, our main objective was to evaluate the safety and clinical and glycemic efficacy of once-weekly semaglutide in

obese patients with T2D and chronic HF during 12 months of follow-up. We also evaluated weight loss and the de-intensification of T2D and HF treatments after the initiation of semaglutide. We hypothesize that the initiation of semaglutide would have beneficial effects on clinical outcomes and glycemic control and is safe in patients with obesity, T2D and chronic HF.

## MATERIALS AND METHODS

We conducted an observational, retrospective, real-world study on obese outpatients with T2D and chronic HF at the HF Units of Internal Medicine Department at the Hospital Regional Universitario de Málaga in Málaga; the Hospital Costal de Sol, in Marbella; and the Hospital Helicopteros Sanitarios, in Marbella, Spain.

Each patient's electronic medical record was reviewed by investigators to gather patient data. The study was approved by the Institutional Research Ethics Committee of Málaga and written informed consent for the consultation of patient medical records was obtained from all participants. This study was conducted in accordance with the Declaration of Helsinki.

### Patients and Study Design

Patients started with a once-weekly dose of 0.25 mg for 4 weeks that could be increased to 0.5 mg for the following 4 weeks until they reached the maintenance dose (0.5 mg or 1.0 mg) provided that the healthcare professionals deemed it advisable according to their clinical judgment. During the follow-up, all patients received general recommendations on a healthy diet and physical activity according to their functional class. Treatment with diuretics, antihypertensive agents, and lipid-lowering drugs were modified, if necessary, as per the healthcare professionals' judgment.

Follow-up was conducted at 3, 6, and 12 months after starting semaglutide. Data on a multitude of anthropometric (body weight, body mass index (BMI), and waist circumference), sociodemographic, clinical (T2D duration and treatment, principal cause of HF, HF duration, left ventricular ejection fraction, previous medical history, and medication), therapeutic (any reduction in the number or doses of T2D and HF drugs), and laboratory variables (serum creatinine, estimated glomerular filtration rate measured using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulae (18), basal fasting blood glucose (BG), glycated hemoglobin (HbA1c), LDL, HDL and total cholesterol, triglycerides, uric acid, hematocrit, N-terminal pro-brain natriuretic peptide (NT-pro-BNP), and urinary albumin/creatinine ratio) were gathered at

each evaluation. The total symptom score on the Spanish version of the Kansas City Cardiomyopathy Questionnaire (KCCQ) (19) and New York Heart Association (NYHA) classification were used to estimate HF health status. Adverse drug reactions, need to discontinue semaglutide due to adverse events, 3-point major adverse cardiovascular events (3P-MACE) (composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death), emergency department visit because of HF decompensation; hospitalizations (HF and all-cause), and mortality (due to cardiovascular or non-cardiovascular causes) after starting semaglutide were also recorded.

## Measured Outcomes

Our primary endpoint was to evaluate the clinical efficacy in the HF health status, as determined by the improvement in the total symptom score on the Spanish version of the Kansas City Cardiomyopathy Questionnaire (KCCQ) (19), reduction in the New York Heart Association (NYHA) classification, and reduction in NT-pro-BNP levels. Secondary outcomes included the glycemic efficacy, as determined by the reduction in HbA1c levels and the proportion of patients who achieved good glycemic control (HbA1c <7%) prior to starting semaglutide and at 3, 6, and 12 months; weight loss (changes in body weight, BMI, and waist circumference); de-intensification of T2D treatment (reduction in number of daily glucose-lowering drugs and/or insulin doses) and HF treatment (decline in number of antihypertensive agents, beta-blockers and diuretics); and the safety (adverse drug reactions, need to discontinue semaglutide due to adverse events, 3P-MACE, emergency department visit because of HF decompensation (from one year before initiation), hospitalizations (from one year before initiation), and mortality (from one year before initiation)).

## Statistical Analyses

Quantitative variables are shown as means  $\pm$  standard deviation whereas qualitative variables are shown as absolute values and percentages. Quantitative variables were compared using Student's *t*-test and the repeated measures analysis of variance whereas qualitative variables were compared using Pearson's chi-square and McNemar's test. The Pearson correlation coefficient was calculated to estimate the linear correlations between variables. Statistical significance was defined as  $p < 0.05$ . Statistical analyses were performed using SPSS Statistics for Windows, version 15.0.

## RESULTS

A total of 136 obese patients with T2D and chronic HF were included in this study. Metformin was the most frequent oral glucose-lowering drug used among the patients (59.6%), followed by dipeptidyl peptidase-4 (DPP-4) inhibitors (39.7%) and SGLT-2 inhibitors (38.2%). Non-semaglutide GLP-1 receptor agonists were used in the 33.8% of the study patients. Basal insulin was used by 86 patients (63.2%) with a mean dose of 39.0 units per day and insulin combinations were used by 16

patients (13.8%) before starting semaglutide. Baseline sociodemographic, clinical, and treatment variables are shown in **Table 1**.

All patients started with an initial once-weekly dose of 0.25 mg for 4 weeks except for patients who previously received GLP-1 receptor agonists, who were switched to 0.50 mg of semaglutide. Once-weekly semaglutide was increased to 1.00mg in 76 patients (59.8%) at 3 months, 93 patients (74.4%) at 6 months, and 100 patients (80.6%) at 12 months.

From baseline to 12 months, there was a significant improvement in the KCCQ total symptom score, which increased from 59.0 points to 79.9 points ( $p < 0.01$ ), as well as a significant reduction in the proportion of patients with NYHA functional class III, which declined from 40.4% to 16.2% ( $p < 0.01$ ), and NT-pro-BNP levels, which declined from  $969.5 \pm 653.5$  to  $577.4 \pm 322.1$  pg/mL ( $p < 0.01$ ). The KCCQ total symptom score correlated negatively with the NT-pro-BNP levels during the follow-up ( $r = -0.687$ ,  $p < 0.01$ ).

In regard to glycemic control, a significant reduction in fasting BG and HbA1c were observed after initiating semaglutide. The proportion of patients with HbA1c <7% increased from 16.2% at baseline to 64.5% at 12 months ( $p < 0.001$ ).

During the follow-up, patients had a significant reduction in body weight (12.7 kg) and BMI ( $7.1 \text{ kg/m}^2$ ), with a decline in the proportion of patients with obesity (BMI  $\geq 30$ ) to 50.8%. There were also significant reductions in the waist circumference and systolic blood pressure. A positive correlation was found between the body weight loss and the KCCQ total symptom score ( $r = 0.612$ ,  $p < 0.01$ ).

Patients who started once-weekly semaglutide experienced a de-intensification in their T2D treatment from baseline to 12 months' follow-up, with declines in the number of daily glucose-lowering drugs ( $3.5 \pm 1.2$  to  $2.2 \pm 0.8$ ,  $p < 0.05$ ), the proportion of patients with basal insulin (63.2% to 32.3%,  $p < 0.001$ ), basal insulin dose ( $39.0 \pm 21.8$  to  $20.2 \pm 8.9$ ,  $p < 0.001$ ), and the proportion of patients with insulin combinations (13.8% to 0,  $p < 0.01$ ). No differences were observed in HF medications.

A significant difference was found in the urinary albumin/creatinine ratio from baseline to 12 months, with a reduction of 39 mg/g. No changes were observed in other laboratory parameters. The urinary albumin/creatinine ratio correlated negatively with the KCCQ total symptom score during the follow-up ( $r = -0.528$ ,  $p < 0.01$ ).

In regard to safety, 30 patients (24.2%) had adverse drug reactions (mostly gastrointestinal disorders) which led to discontinuation of semaglutide in 12 of them (11 patients due to gastrointestinal disorders). There were six 3P-MACEs linked to two cardiovascular deaths. Emergency department visits due to HF, hospitalizations due to HF, and all-cause hospitalizations were lower 12 months after starting semaglutide compared to the data reported in the 12 months before starting semaglutide (50.7% vs. 39.5%,  $p < 0.05$ ; 38.2% vs 27.4%,  $p < 0.05$ ; and 8.8% vs 4.0%,  $p < 0.05$ ; respectively).

All data on clinical efficacy in the HF health status, glycemic control, anthropometric characteristics, treatment de-

**TABLE 1 |** Baseline sociodemographic and clinical-therapeutic characteristics.

Variables	n = 136
Sociodemographic characteristics	
Age (years)	72.6 ± 11.0
Male gender	74 (54.4%)
Diabetes characteristics	
Diabetes duration (years)	13.5 ± 7.4
Diabetes therapy	81 (59.6%)
Metformin	4 (2.9%)
Sulfonylurea	54 (39.7%)
DPP-4 inhibitor/GLP-1 receptor agonist (no semaglutide)	46 (33.8%)
SGLT-2 inhibitor	52 (38.2%)
Basal insulin	86 (63.2%)
Basal insulin dose (Units/day)	39.0 ± 21.8
Insulin combinations	16 (13.8%)
Statins	122 (89.7%)
Heart failure characteristics	
Heart failure duration (years)	6.5 ± 3.2
Principal cause of heart failure	
Ischemic	56 (41.2%)
Non-ischemic	80 (58.8%)
Left ventricular ejection fraction (%)	52.5 ± 10.9
Left ventricular ejection fraction <40%	54 (39.7%)
Heart failure medication	
Diuretic	134 (98.8%)
ACE inhibitor	24 (16.9%)
ARB	62 (45.6%)
Sacubitril-valsartan	34 (25.0%)
Beta-blocker	102 (75.0%)
Ivabradin	25 (18.3%)
Mineralocorticoid receptor antagonist	59 (43.4%)
Digitalis	16 (11.8%)
Anticoagulant	72 (52.9%)
Previous medical history	
History of smoking	76 (55.9%)
History of alcohol abuse	13 (9.6%)
Hypertension	136 (100.0%)
Dyslipidaemia	124 (91.2%)
Chronic kidney disease stage ≥3	88 (64.7%)
Cerebrovascular disease	15 (11.0%)
Chronic obstructive pulmonary disease	34 (25.0%)
Atrial fibrillation	62 (45.6%)

Continuous data are shown as means (standard deviations) and qualitative data as absolute value and percentage.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter 2.

intensification, laboratory variables, and safety are summarized in **Table 2**.

No significant differences were found in the KCCQ total symptom score, NT-pro-BNP levels, fasting BG, HbA1c, and body weight during the follow-up period according to estimated glomerular filtration rate (<60 vs ≥60 ml/min/1.73 m<sup>2</sup>). All these data shown in **Table 3**.

## DISCUSSION

This study found that obese patients with T2D and chronic HF who were treated with once-weekly semaglutide improved their HF health status, increasing the quality of life and reducing the functional class and the NT-proBNP levels. Semaglutide was also efficacious in regard to glycemic control, with reductions in fasting BG and HbA1c levels and body weight. In addition,

patients treated with semaglutide experienced a significant de-intensification of T2D treatment, with reductions in the number of daily glucose-lowering drugs, basal insulin doses, and proportion of patients with insulin therapy, with a good tolerability profile. Semaglutide was also associated with reductions in emergency department visits due to HF, hospitalizations due to HF, and all-cause hospitalizations.

The coexistence of chronic HF with T2D is common and T2D is considered one of the significant risk factor for adverse outcomes in patients with HF (2–4). In recent years, the cardiovascular safety of glucose-lowering drugs, especially with SGLT-2 inhibitors and GLP-1 receptor agonists, has become an important topic and several cardiovascular outcome trials have been performed. Whereas SGLT-2 inhibitors have clearly shown benefits in HF hospitalizations in patients with (20–24) and without T2D (25, 26), GLP-1 receptor agonists have not been demonstrated to lead to significant reductions in HF

**TABLE 2 |** Clinical efficacy in the heart failure health status, glycemic control, anthropometric characteristics, treatment de-intensification, laboratory variables, and safety.

Variables	Baseline (n = 136)	3 months' follow-up (n = 127)	6 months' follow-up (n = 125)	12 months' follow-up (n = 124)
HF health status				
KCCQ total symptom score	59.0 ± 24.1	68.9 ± 25.1*	75.5 ± 27.5 <sup>†</sup>	79.7 ± 28.4 <sup>‡</sup>
NYHA functional class				
I	0	0	6 (4.8%)	7 (5.6%)
II	81 (59.6%)	88 (69.3%)	94 (75.2%) <sup>†</sup>	97 (78.2%) <sup>‡</sup>
III	55 (40.4%)	*39 (30.7%)*	25 (20.0%) <sup>†</sup>	20 (16.2%) <sup>‡</sup>
NT-proBNP (pg/mL)	969.5 ± 653.5	738.8 ± 553.4*	610.9 ± 424.5 <sup>†</sup>	577.4 ± 322.1 <sup>‡</sup>
Glycemic control				
Fasting blood glucose (mg/dL)	154.9 ± 50.0	140.4 ± 42.2 <sup>†</sup>	121.5 ± 38.4 <sup>‡</sup>	117.0 ± 33.2 <sup>‡</sup>
HbA1c (%)	8.1 ± 1.4	7.3 ± 1.2*	7.0 ± 1.1 <sup>†</sup>	6.7 ± 1.0 <sup>†</sup>
Patients with HbA1c <7%	22 (16.2)	45 (35.4%)*	66 (52.8%) <sup>‡</sup>	80 (64.5%) <sup>‡</sup>
Anthropometric characteristics				
Body weight (kg)	97.8 ± 19.7	92.8 ± 16.7*	87.1 ± 14.4 <sup>†</sup>	85.1 ± 13.2 <sup>‡</sup>
Body Mass Index (kg/m <sup>2</sup> )	36.6 ± 7.2	33.9 ± 6.5*	30.9 ± 4.9 <sup>†</sup>	29.5 ± 4.3 <sup>‡</sup>
Body Mass Index ≥30	136 (100.0%)	103 (81.1%)*	80 (64.0%) <sup>†</sup>	61 (49.2%) <sup>‡</sup>
Waist circumference (cm)	133.3 ± 19.1	119.1 ± 15.2*	108.8 ± 12.7 <sup>†</sup>	102.9 ± 10.0 <sup>‡</sup>
SBP (mmHg)	130.9 ± 12.3	122.4 ± 11.1	119.2 ± 10.4*	118.4 ± 10.0*
DBP (mmHg)	72.5 ± 13.6	71.5 ± 12.8	69.1 ± 9.9	68.4 ± 8.9
Heart rate (bpm)	75.1 ± 12.6	72.4 ± 10.2	70.2 ± 8.9	69.7 ± 8.2
Treatment de-intensification				
Number of daily antidiabetic agents	3.5 ± 1.2	2.5 ± 0.9*	2.4 ± 0.9*	2.2 ± 0.8*
Basal insulin	86 (63.2%)	70 (55.1%)*	48 (38.4%) <sup>†</sup>	40 (32.3%) <sup>‡</sup>
Basal insulin dose (Units/day)	39.0 ± 21.8	32.9 ± 18.5*	24.6 ± 11.0 <sup>†</sup>	20.2 ± 8.9 <sup>‡</sup>
Insulin combinations	16 (13.8%)	9 (7.1%)*	1 (0.8%) <sup>†</sup>	0 <sup>†</sup>
Laboratory variables				
Creatinine (mg/dL)	1.2 ± 0.5	1.2 ± 0.5	1.3 ± 0.5	1.3 ± 0.5
EGFR (ml/min/1.73 m <sup>2</sup> )	56.8 ± 22.4	55.9 ± 21.2	56.4 ± 22.8	57.7 ± 22.9
Uric acid (mg/dL)	7.7 ± 5.0	7.1 ± 4.8	6.8 ± 3.8	6.7 ± 3.5
Hematocrit (%)	41.7 ± 5.5	43.0 ± 5.8	43.6 ± 6.3	43.7 ± 6.4
LDL cholesterol (mg/dL)	78.4 ± 28.5	77.4 ± 24.5	70.7 ± 21.1	71.5 ± 21.2
HDL cholesterol (mg/dL)	40.4 ± 9.5	39.8 ± 9.1	41.1 ± 10.5	43.1 ± 12.0
Total cholesterol (mg/dL)	158.7 ± 39.2	159.9 ± 39.5	147.6 ± 40.0	151.4 ± 44.4
Triglycerides (mg/dL)	203.9 ± 60.0	197.3 ± 56.4	200.5 ± 58.1	207.4 ± 59.1
Urinary albumin/creatinine ratio (mg/g)	52.4 ± 47.8	46.4 ± 40.8*	23.6 ± 12.8 <sup>†</sup>	13.4 ± 9.9 <sup>‡</sup>
Safety variables <sup>a</sup>				
Adverse drug effects	–	12 (9.4%)	25 (20.0%)	30 (24.2%)
Gastrointestinal disorder	–	12	24	30
Nausea	–	5	11	14
Vomiting	–	4	8	10
Diarrhea	–	3	5	6
Acute pancreatitis	–	0	1	0
Discontinuation of semaglutide	–	9 (6.6%)	11 (8.1%)	12 (8.8%)
Major complication <sup>a,b</sup>				
3P-MACE	–	0	2 (1.6%)	6 (4.8%)
Emergency department visit because of HF	69 (50.7%)	20 (15.7%)	30 (24.0%)	49 (39.5%)*
Hospitalization				
Because of HF	52 (38.2%)	10 (7.9%)	19 (15.2%)	34 (27.4%)*
All-cause	12 (8.8%)	2 (1.6%)	3 (2.4%)	5 (4.0%)*
Mortality	–			
Cardiovascular cause	–	0	0	2 (2.4%)
Noncardiovascular cause	–	0	0	0
HF hospitalization and cardiovascular mortality	–	10 (7.9%)	19 (15.2%)	36 (29.0%)

Continuous data are shown as means (standard deviations) and qualitative data as absolute value and percentages. Statistical significance was measured for the comparison of baseline and follow-up data.

DBP, diastolic blood pressure; EGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; 3P-MACE, 3-Point major adverse cardiovascular event; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure

<sup>a</sup>Cumulative data during the 12 months of follow-up are shown.

<sup>b</sup>Data from one year before initiation (baseline) were compared with 3, 6, and 12 months' follow-up.

\* $p < .05$ .

<sup>†</sup> $p < .01$ .

<sup>‡</sup> $p < .001$ .

**TABLE 3 |** Kansas City Cardiomyopathy Questionnaire total symptom score, N-terminal pro-brain natriuretic peptide levels, fasting blood glucose, glycated hemoglobin, and body weight according to estimated glomerular filtration rate.

Variables	EGFR	Baseline (n = 136)	3 months' follow-up (n = 127)	6 months' follow-up (n = 125)	12 months' follow-up (n = 124)
KCCQ total symptom score	<60 ml/min/1.73 m <sup>2</sup>	58.1 ± 24.0	68.1 ± 24.8	74.9 ± 27.1	79.5 ± 28.3
	EGFR ≥60 ml/min/1.73 m <sup>2</sup>	59.9 ± 24.3	69.7 ± 25.4	76.1 ± 27.8	79.9 ± 28.5
p-value		0.187	0.201	0.198	0.298
NT-proBNP (pg/mL)	<60 ml/min/1.73 m <sup>2</sup>	949.5 ± 651.1	713.6 ± 547.9	598.6 ± 420.7	571.0 ± 318.9
	EGFR ≥60 ml/min/1.73 m <sup>2</sup>	989.1 ± 659.2	764.0 ± 563.4	623.2 ± 429.2	583.8 ± 326.2
p-value		0.164	0.101	0.111	0.179
Fasting BG (mg/dL)	<60 ml/min/1.73 m <sup>2</sup>	156.4 ± 50.8	140.8 ± 42.4	122.5 ± 38.6	118.5 ± 33.5
	EGFR ≥60 ml/min/1.73 m <sup>2</sup>	153.4 ± 49.3	140.0 ± 42.0	120.5 ± 38.0	115.5 ± 32.8
p-value		0.242	0.301	0.238	0.237
HbA1c (%)	<60 ml/min/1.73 m <sup>2</sup>	8.2 ± 1.5	7.4 ± 1.3	7.1 ± 1.1	6.9 ± 1.2
	EGFR ≥60 ml/min/1.73 m <sup>2</sup>	8.1 ± 1.4	7.2 ± 1.2	7.0 ± 1.1	6.7 ± 1.0
p-value		0.302	0.289	0.311	0.291
Body weight (kg)	<60 ml/min/1.73 m <sup>2</sup>	96.8 ± 19.2	92.3 ± 16.4	86.6 ± 14.2	84.6 ± 13.1
	EGFR ≥60 ml/min/1.73 m <sup>2</sup>	98.8 ± 19.9	93.3 ± 16.8	87.6 ± 14.5	85.5 ± 13.2
p-value		0.199	0.283	0.295	0.300

Continuous data are shown as means (standard deviations) and qualitative data as absolute value and percentages. Statistical significance was measured for the comparison of EGFR groups.

BG, blood glucose; EGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-brain natriuretic peptide.

hospitalizations (9–16). However, when all patients from all GLP-1 receptor agonists' trials were analysed in a meta-analysis carried out by Kristensen et al. (17), GLP-1 receptor agonists were associated with a significant reduction in HF hospitalizations. Recently, a systematic review of observational studies found conflicting results in terms of HF outcomes of GLP-1 receptor agonists, with some studies showing lower rates of HF hospitalization among GLP-1 receptor agonists' users and other studies showing neutral effects on HF hospitalizations (27). One of these studies that showed benefits was a retrospective cohort of 1,426 users of GLP-1 receptor agonists and 2,798 control subjects. After a propensity score matched analysis, the use of GLP-1 drugs were associated with a risk reduction of 49% in HF hospitalization. There were also significant reductions in all-cause hospitalization (46%) and deaths (69%) (28). In another study that prospectively included 288 patients with T2D and chronic HF treated with cardiac resynchronization therapy with a defibrillator, the use of GLP-1 receptor agonists in addition to conventional hypoglycemic therapy was associated with a significant decline in NYHA class, higher scores on the 6-minute walking test, and a higher probability of the patients responding to cardiac resynchronization therapy with a defibrillator. Additionally, GLP-1 receptor agonist users experienced fewer arrhythmic events, a lower rate of hospitalization for HF worsening, and a higher probability of the patient responding to cardiac resynchronization therapy with a defibrillator in the follow-up period (29).

These benefits on HF outcomes are consistent with our results. In our study, the use of semaglutide was associated with improvement in HF health status, increasing the quality of life and reducing the functional class. As secondary outcomes,

we also observed benefits associated with the use of semaglutide in reductions in emergency department visits due to HF, hospitalizations due to HF and all-cause hospitalizations.

Although at present there are not studies reporting benefits of once-weekly semaglutide on HF outcomes focused on patients with HF, in the SUSTAIN-6 trial -the pivotal cardiovascular outcome trial of subcutaneous semaglutide in patients with T2D and high cardiovascular risk (23.6% with HF)- no significant benefits were observed in hospitalizations for HF when compared with placebo group (11).

Several drugs routinely used in HF, such as angiotensin-converting enzyme inhibitors, angiotensin receptor-neprilysin inhibitor, beta-blockers, and mineralocorticoid receptor antagonists, have been associated with greater survival, a reduction in the risk of HF hospitalization, and a reduction in symptoms in patients with HF with reduced ejection fraction (30). Recently, SGLT-2 inhibitors have also shown robust benefits in HF hospitalizations in patients with HF with reduced ejection fraction regardless of the presence of T2D in the DAPA-HF (dapagliflozin) (25) and EMPEROR-Reduced (empagliflozin) (26) clinical trials. Furthermore, positive results have been shown in the EMPEROR-Preserved trial (31), a clinical trial on empagliflozin versus a placebo in patients with HF with preserved ejection fraction regardless of presence of T2D. Empagliflozin was associated with a significant decline in the composite variable of cardiovascular death or hospitalization due to HF. A recent meta-analysis also found a significant association between SGLT-2 inhibitors and an improvement in health-related quality of life (32).

In our study, we also observed a reduction of NT-proBNP levels with the use of semaglutide. This benefit has been

previously observed in a study using liraglutide on patients with T2D and HF with reduced ejection fraction (33).

The benefits on HF outcomes observed with the use of GLP-1 receptor agonists may be due to their direct effects through actions on endothelial dysfunction and inflammation (34), reducing the circulating immune cell and chemokine levels, the vascular expression of pro-inflammatory mediators and leukocyte adhesion molecules, and the vascular infiltration by immune cells (35). GLP-1 receptor agonists have been shown to modulate water and sodium homeostasis, reducing hyperfiltration and increasing natriuresis (36). Other potential protective mechanisms include their effects on the renin-angiotensin system, principally a reduction in renin-angiotensin-aldosterone system activation markers (37). GLP-1 receptor agonists may have indirect cardiorenal protective benefits given their effects on improving blood pressure due to atrial natriuretic peptide release from atrial cardiomyocytes and nitric oxide production (35), and glycemic control, increasing insulin sensitivity, and reducing insulin levels. The sustained weight loss associated with GLP-1 receptor agonists and the potential impacts on the gut microbiota composition may also be potential beneficial factors (34, 37). Furthermore, GLP-1 receptors have been found in the heart. The action of GLP-1 may favor myocardial glucose uptake regardless the insulin secretion *via*, ameliorating insulin resistance associated with HF though the up-regulation of GLP-1 isoforms such as sarcolemmal and endosome Glut4. GLP-1 cardiomyocyte-independent actions may improve coronary flow and left ventricular wall motion, improving myocardial function (35, 38–40). The adipose tissue metabolome has been also described as modifiable regulators of vascular redox state in obese patients, directly impacting on cardiovascular outcomes in patients with established atherosclerosis (41). In addition, treatment with a GLP-1 receptor agonist such as liraglutide has been associated with a maintained reduction in apoB levels, potentially contributing to a lower cardiovascular risk (42). An endogenous GLP-1 response induced by oral glucose has been associated with clinically relevant lower central and peripheral blood pressures, which may also contribute to a decreased cardiovascular risk (43). In our study, the improvement in glycemic control (reduction of 1.4% in HbA1c at 12 months of follow-up) and reduction in body weight (weight loss of 12.7 kg at 12 months of follow-up) may also be potential factors involved in the benefits on the HF health status outcomes. Recently, a strategy combining moderate-to-vigorous-intensity exercise and liraglutide therapy led to greater weight loss than exercise or liraglutide alone in patients with obesity. The combination strategy was also associated with improvements in the HbA1c level, insulin sensitivity, and cardiorespiratory fitness (44). This finding shows the importance of implementing structured treatment programs using GLP-1 receptor agonists in combination with exercise in order to achieve long-term weight loss goals and health benefits. Moreover, the use of insulin has been described as a drug that could worsen HF (45). We observed a significant reduction in the proportion of patients with insulin after starting once-weekly semaglutide. This finding

may also contribute to the clinical benefit observed in obese patients with T2D and HF.

All these potential cardiovascular benefits in obese patients with T2D and HF could be also extrapolated to patients without T2D. Long-term efficacy and safety have been shown for GLP-1 receptor agonists as anti-obesity drugs (46).

Another relevant finding from our study was the de-intensification of the antidiabetic treatment, with fewer daily glucose-lowering drugs. Treatment simplification is especially important in patients with T2D and HF, who are normally subject to polypharmacy and more likely to have adverse drug reactions (45, 47). Simplification of the antidiabetic treatment have been recently shown with the SGLT-2 inhibitor canagliflozin in patients with HF and T2D, with significant reduction in number of glucose-lowering drugs, basal insulin dose, and percentage of patients who used basal insulin after switching non-insulin glucose lowering drugs (excluding metformin) to canagliflozin (48).

Though our results are important, this study has several limitations. First, the observational nature of our data, the limited number of patients, and the lack of a control group might have led to bias. Second, considering the low number of complications or events, their relationship to the use of semaglutide could not be conclusively determined. Third, as the HF medication could be modified if deemed advisable according to healthcare providers' judgment together with the fact that patients were given general recommendations during follow-up on a healthy diet and physical activity suitable to their functional class, the entirety of our findings cannot be strictly attributed to initiating semaglutide. Finally, only once-weekly semaglutide was evaluated in our study. Due to these limitations, our findings cannot be extrapolated to other GLP-1 receptor agonists.

In conclusion, the use of once-weekly semaglutide improved HF health status, increasing quality of life and reducing functional class and NT-proBNP levels in obese patients with T2D and chronic HF. Semaglutide was also efficacious in regard to glycemic control and body weight reduction. In addition, patients treated with semaglutide experienced a significant de-intensification of T2D treatment, with a good tolerability profile. Reductions emergency department visits due to HF, hospitalizations due to HF, and all-cause hospitalizations were also observed. Randomized clinical trials with GLP-1 receptor agonists are required to provide more evidence on the efficacy and safety of GLP-1 receptor agonists in patients with HF.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Research Ethics Committee of Málaga.

The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

LP-B and JS-C contributed to the conception, design of the work the acquisition, interpretation of data, writing-original draft preparation, writing-review and editing, and supervision. MG, MR, BA-B, LC-P, MP-V, AL-S, MB-L, SJ-C, and JM-G contributed to the acquisition of data and revised the work. JS-C contributed to interpretation of data, writing-review and editing, and supervision. RG-H was a major contributor in interpretation of data, writing-original draft preparation, writing-review and editing, and supervision. All authors read

and approved the final manuscript. All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

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