Scientific letters

Once weekly semaglutide and cardiovascular outcomes in patients with type 2 diabetes and heart failure with reduced left ventricular ejection fraction

Semaglutida semanal y objetivos cardiovasculares en pacientes con diabetes mellitus tipo 2 e insuficiencia cardiaca con FAVI reducida

To the Editor,

In recent years, sodium-glucose cotransporter 2 inhibitors (SGLT2i) have demonstrated significant heart failure (HF) benefits in patients with HF with reduced ejection fraction (HFrEF) regardless of the presence of type 2 diabetes (T2D).[1] Glucagon-like peptide-1 receptor agonists (GLP-1ra) have also been shown to significantly reduce hospitalizations for HF in patients with T2D in a meta-analysis of pivotal cardiovascular clinical trials, although these benefits were not achieved in each individual clinical trial.[2] Furthermore, the evidence provided by observational studies is fairly limited and controversial.[3]

We performed a prospective, multicenter, real-world study in patients with T2D and HFrEF treated with semaglutide (Sema-Reduced-Group) and without semaglutide or another GLP-1ra (control-reduced-group) and followed up for 52 weeks between June 2019 and May 2023.

The diagnosis of HFrEF was established according to the 2021 European Society of Cardiology Guidelines.[4]

Data on multiple clinical variables were gathered at each evaluation.

The primary outcome was the number of HF events (a composite of emergency department visits, hospitalizations, and unscheduled outpatient visits). Secondary outcomes included the individual components of the primary outcome, cardiovascular death, all-cause death, all-cause hospitalizations, new or worsening nephropathy, and $\geq$ 5-point difference in the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score change from baseline to 52 weeks of follow-up.

To match each patient in each group in a 1:1 manner, we used propensity score matching (PSM). The adequacy of the PSM was assessed using the standardized difference (a significant imbalance was considered with a standardized difference $>$ 10% between baseline variables). The probability of starting semaglutide was estimated using a logistic regression model. The Pearson correlation coefficient was calculated to estimate linear correlations. To evaluate the association between treatment and study outcomes, mixed effect logistic regressions were used and adjusted for confounding variables.

A total of 202 patients were included in the sema-reduced-group, and 162 patients in the control-reduced-group. After PSM, 122 patients were included in each group. At 52 weeks, 104 patients (85.2%) had received 1.00 mg of once weekly semaglutide. Baseline characteristics are shown in table 1.

Once weekly semaglutide was associated with reductions in HF events and their individual components. Furthermore, cardiovascular death and all-cause hospitalizations decreased significantly. Last, patients in the sema-reduced-group were more likely to have a $\geq$ 5-point difference on the KCCQ score change (improving 18.7 $\pm$ 3.2 vs 8.2 $\pm$ 1.7 points ($P < .01$) compared with the control-reduced-group. Outcomes results are shown in table 2.

Patients treated with semaglutide had a larger reduction in HbA1c (0.9 $\pm$ 0.2 vs 0.3 $\pm$ 0.1%, $P = .011$) and body weight (11.8 $\pm$ 3.8 vs 2.5 $\pm$ 1.1 kg, $P < .01$) than those in the control-reduced-group. There were negative correlations between the KCCQ score and HbA1c (r = 0.532, $P < .009$) and body weight (r = –0.649, $P < .01$).

Regarding safety, fewer serious adverse events occurred among patients who received semaglutide (24.6%). Adverse events were mostly gastrointestinal, and 11 patients (9.0%) discontinued the drug.

While SGLT2i have shown benefits in HF outcomes in patients with HF with and without T2D, GLP-1ra have not been strongly associated with reductions in HF hospitalizations.[2] The evidence from observational studies is fairly limited and controversial, being associated with neutral effects in some studies and beneficial effects, namely a reduction in HF hospitalizations, in other studies.[3] Recently, once weekly semaglutide has been associated with cardiovascular and HF benefits in overweight/obese patients with pre-existing cardiovascular disease,[5] and HF with preserved ejection fraction.[6] The HF benefits of GLP-1ra could be achieved through multiple interrelated mechanism such as the direct effects on endothelium, cardiac tissue, renin-angiotensin system, and cardiometabolic risk factors.[3,5]

The above-mentioned benefits on HF outcomes found in several studies (some including patients with HFrEF with coronary artery and cerebrovascular diseases) are consistent with our results. The implementation of structured treatment programs including the use of GLP-1ra in combination with improvements in the quality of diet and exercise to achieve long-term body weight loss and an increase in lean mass could be established as an important goal in the management of patients with T2D, overweight/obesity, and HFrEF.

Although these findings provide valuable information, they should be considered within the context of potential limitations such as the possibility of unmeasured confounding factors, the relatively low number of some outcomes, and the influence of changes in HF treatment and general recommendations made during the follow-up.

In conclusion, in this observational study and after a PSM, once weekly semaglutide was associated with a reduction in HF events, cardiovascular death, and all-cause hospitalizations in patients with T2D and HFrEF. Furthermore, patients treated with semaglutide were more likely to have a $\geq$ 5-point difference on the KCCQ total symptom score from baseline to 52 weeks. Further research is needed on GLP-1ra in HFrEF.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ETHICAL CONSIDERATIONS

The study was approved by the Institutional Research Ethics Committee of Málaga (Ethics Committee code: REDIME-27-10-

Table 1
Sociodemographic, clinical, and therapeutic characteristics at baseline: pre- and postpropensity score matching analysis

	Prepropensity score matching analysis				Postpropensity score matching analysis			
Variables	Sema-reduced-group (n = 202)	Control-reduced-group (n = 162)	Standardized difference	*P*	Sema-reduced-group (n = 122)	Control-reduced-group (n = 122)	Standardized difference	*P*
Sociodemographic characteristics								
Age, y	70.4 ± 10.2	72.1 ± 11.0	.055	.181	70.7 ± 10.4	72.0 ± 11.0	0.051	.188
Male sex	106 (52.5%)	88 (54.3%)	.077	.169	65 (53.3%)	66 (54.1%)	0.082	.196
Anthropometric characteristics								
Body weight, kg	92.6 ± 17.0	85.2 ± 15.2	.112	.031	91.0 ± 16.4	87.9 ± 15.9	0.083	.078
Body Mass Index, kg/m²	32.1 ± 5.5	28.8 ± 5.3	.107	.044	31.5 ± 5.2	29.6 ± 5.0	0.079	.101
Obesity, body mass index ≥ 30	202 (100.0%)	108 (66.7%)	.119	.018	122 (100.0%)	105 (86.1%)	0.089	.070
Waist circumference, cm	127.4 ± 17.2	119.1 ± 15.9	.120	.013	124.5 ± 17.0	120.4 ± 16.1	0.072	.099
SBP, mmHg	127.5 ± 11.4	123.2 ± 10.4	.085	.106	126.5 ± 11.2	124.8 ± 10.8	0.078	.122
DBP, mmHg	72.0 ± 10.2	70.0 ± 9.7	.019	.204	72.0 ± 10.2	71.1 ± 9.9	0.017	.235
Heart rate, bpm	71.0 ± 10.5	69.5 ± 10.0	.022	.198	70.8 ± 10.2	69.8 ± 10.0	0.020	.201
Diabetes characteristics								
Diabetes duration, y	12.1 ± 7.0	10.8 ± 6.1	.090	.105	11.8 ± 6.8	11.0 ± 6.2	0.072	.185
Patients with HbA1c < 7%	15 (7.4%)	40 (25.0%)	.131	.009	14 (11.5%)	22 (18.0%)	0.081	.079
Diabetes therapy			.088	.098			0.072	.111
Metformin	115 (56.9%)	97 (60.0%)			70 (57.4%)	73 (59.8%)		
Sulfonylurea	4 (2.0%)	6 (3.7%)			3 (2.5%)	4 (3.3%)		
DPP-4 inhibitor	79 (39.1%)	70 (43.2%)			49 (40.2%)	51 (41.8%)		
GLP-1 receptor agonist, no semaglutide	52 (25.7%)	0			31 (25.4%)	0		
SGLT-2 inhibitor	122 (60.4%)	91 (56.2%)			71 (58.2%)	69 (56.6%)		
Baseline insulin	75 (37.1%)	54 (33.3%)			43 (35.2%)	41 (33.6%)		
Baseline insulin dose, units/d	17.0 ± 14.4	16.0 ± 14.1			17.0 ± 14.2	16.2 ± 14.1		
Insulin combinations	15 (7.4%)	14 (8.6%)			10 (8.2%)	10 (8.2%)		
Statins	184 (91.1%)	146 (90.1%)	.030	.231	111 (91.0%)	111 (91.0%)	0.012	.254
Heart failure characteristics								
Heart failure duration, y	7.2 ± 3.3	7.5 ± 3.5	.039	.138	7.3 ± 3.4	7.4 ± 3.5	0.022	.189
Principal cause of heart failure			.059	.147			0.028	.184
Ischemic	171 (84.7%)	130 (80.2%)			102 (83.6%)	100 (82.0%)		
Nonischemic	31 (15.3%)	32 (19.8%)			20 (16.4%)	22 (18.0%)		
KCCQ total symptom score	63.7 ± 24.5	64.1 ± 24.6	.028	.255	63.9 ± 24.6	64.0 ± 24.6	0.011	.286
NYHA functional class			.051	.162			0.005	.302
I	0	0			0	0		
II	132 (65.3%)	107 (66.0%)			80 (65.6%)	80 (65.6%)		
III	70 (34.7%)	55 (34.0%)			42 (34.4%)	42 (34.4%)		
Left ventricular ejection fraction, %	37.0 ± 7.2	38.2 ± 8.5	.041	.212	37.5 ± 7.3	38.0 ± 8.4	0.018	.296

Table 1 *(Continued)*
Sociodemographic, clinical, and therapeutic characteristics at baseline: pre- and postpropensity score matching analysis

	Prepropensity score matching analysis				Postpropensity score matching analysis			
Variables	Sema-reduced-group (n = 202)	Control-reduced-group (n = 162)	Standardized difference	*P*	Sema-reduced-group (n = 122)	Control-reduced-group (n = 122)	Standardized difference	*P*
Heart failure medication			.061	.137			0.052	.151
Diuretic	171 (84.7%)	136 (84.0%)			103 (84.4%)	103 (84.4%)		
ACE inhibitor	20 (9.9%)	20 (12.3%)			13 (10.7%)	14 (11.5%)		
ARB	66 (32.7%)	51 (31.5%)			39 (32.0%)	39 (32.0%)		
Sacubitril-valsartan	101 (50.0%)	82 (50.6%)			61 (50.0%)	61 (50.0%)		
Beta-blocker	174 (86.1%)	145 (89.5%)			106 (86.9%)	108 (88.5%)		
Ivabradin	67 (33.2%)	51 (31.5%)			39 (32.0%)	39 (32.0%)		
Mineralocorticoid receptor antagonist	112 (55.4%)	94 (58.0%)			103 (84.4%)	103 (84.4%)		
Digitalis	30 (14.9%)	27 (16.7%)			19 (15.6%)	20 (16.4%)		
Anticoagulant	96 (47.5%)	75 (46.3%)			57 (46.7%)	57 (46.7%)		
Previous medical history								
History of smoking	116 (57.4%)	86 (53.1%)	.057	.141	68 (55.7%)	66 (54.1%)	0.041	.159
History of alcohol abuse	21 (10.4%)	16 (9.9%)	.036	.195	12 (9.8%)	12 (9.8%)	0.019	.285
Hypertension	194 (96.0%)	155 (95.7%)	.045	.173	117 (95.9%)	117 (95.9%)	0.008	.311
Dyslipidemia	196 (97.0%)	146 (90.1%)	.039	.258	115 (94.3%)	111 (91.0%)	0.027	.262
Chronic kidney disease stage ≥ 3	111 (55.0%)	98 (60.5%)	.059	.156	69 (56.6%)	72 (59.0%)	0.041	.172
Cerebrovascular disease	32 (15.8%)	17 (10.5%)	.062	.124	17 (13.9%)	14 (11.5%)	0.051	.147
Chronic obstructive pulmonary disease	60 (29.7%)	38 (23.5%)	.041	.202	34 (27.9%)	31 (25.4%)	0.038	.211
Atrial fibrillation	88 (43.6%)	78 (48.1%)	.040	.185	54 (44.3%)	57 (46.7%)	0.039	.193
Laboratory variables								
Glucose, mg/dL	147.5 ± 40.2	140.0 ± 36.5	.089	.087	144.2 ± 40.0	141.3 ± 37.7	0.073	.102
HbA1c, %	7.5 ± 1.2	7.0 ± 1.0	.109	.044	7.4 ± 1.2	7.2 ± 1.1	0.078	.112
Creatinine, mg/dL	1.1 ± 0.6	1.1 ± 0.7	.022	.214	1.1 ± 0.6	1.1 ± 0.7	0.021	.219
EGFR, mL/min/1.73 m²	52.9 ± 22.0	56.4 ± 23.0	.038	.161	53.5 ± 22.3	55.1 ± 22.8	0.040	.179
Uric acid, mg/dL	6.6 ± 4.6	6.1 ± 4.5	.035	.180	6.4 ± 4.5	6.2 ± 4.5	0.021	.217
Hematocrit, %	42.8 ± 6.1	41.0 ± 5.3	.030	.171	42.2 ± 6.1	41.5 ± 5.4	0.028	.182
NT-proBNP, pg/mL	1152.8 ± 646.2	910.0 ± 589.2	.057	.141	1050.5 ± 636.0	922.5 ± 599.0	0.042	.167
LDL-C, mg/dL	65.0 ± 21.3	70.3 ± 25.2	.059	.150	67.0 ± 21.3	69.5 ± 24.6	0.039	.175
HDL-C, mg/dL	43.5 ± 9.9	39.8 ± 9.4	.038	.177	41.5 ± 9.5	39.9 ± 9.4	0.037	.179
Total cholesterol, mg/dL	143.5 ± 36.2	151.7 ± 40.7	.062	.138	148.9 ± 37.7	150.5 ± 40.2	0.053	.158
Triglycerides, mg/dL	150.0 ± 52.0	161.0 ± 55.5	.071	.122	155.4 ± 53.0	159.0 ± 55.0	0.070	.129
Urinary albumin/creatinine ratio, mg/g	50.0 ± 42.0	45.1 ± 40.0	.070	.133	49.4 ± 41.4	47.5 ± 40.5	0.061	.145

Continuous data are shown as means ± standard deviation and qualitative data as No. (%). The differences between groups were determined using the 2-sample Student *t*-test or the Mann-Whitney-Wilcoxon rank-sum test for continuous variables and Pearson's chi-square for categorical variables.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; DPP4, dipeptidyl peptidase-4; EGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT-2, sodium-glucose cotransporter 2.

Table 2
Primary and secondary outcomes

Outcomes	Sema-reduced-group (n = 122)	Control-reduced-group (n = 122)	Mixed effect logistic regression	
			OR (95%CI)	*P*
Heart failure event	30 (24.6)	45 (36.9)	0.82 (0.61-0.99)	.009
Emergency department visits due to heart failure decompensation	21 (17.2)	33 (27.0)	0.85 (0.68-0.99)	.028
Hospitalization due to heart failure	17 (13.9)	29 (23.8)	0.84 (0.69-0.99)	.020
Unplanned outpatient visits	21 (17.2)	34 (27.9)	0.87 (0.69-0.99)	.042
Cardiovascular death	13 (10.7)	27 (22.1)	0.89 (0.70-0.99)	.044
All-cause death	19 (15.6)	29 (23.8)	0.93 (0.86-1.19)	.093
All-cause hospitalizations	25 (20.5)	39 (31.9)	0.86 (0.63-0.99)	.014
New or worsening nephropathy[*]	4 (3.3)	8 (6.6)	0.94 (0.67-1.12)	.082
≥ 5-point difference in the KCCQ change (from baseline to 52 weeks)	50 (41.0)	16 (13.1)	2.38 (1.24-5.20)	< .01

Data are shown as No. (%). To evaluate the association between treatment and study outcomes, mixed effect logistic regressions were used. The regression analysis values are expressed as odds ratio and 95% confidence interval. Values were considered statistically significant if $P < .05$.
95%CI, 95% confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire; OR, odds ratio.
[*] Defined by persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of < 45 mL/min/1.73 m^2, or the need for continuous renal replacement therapy.

2016) and written informed consent for the consultation of medical records was obtained from all participants. This study was conducted in accordance with the Declaration of Helsinki. Data confidentiality and patient anonymity were rigorously maintained during the performance of the study.

Gender disaggregation was not performed based on the outcomes of this study.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence was used in the preparation of this article.

AUTHORS' CONTRIBUTIONS

M.A. Pérez-Velasco: analysis and interpretation of data and manuscript preparation. A. Trenas: analysis and interpretation of data and manuscript preparation. M.R. Bernal-López: analysis and interpretation of data and manuscript preparation. M.D. García de Lucas: analysis and interpretation of data and manuscript preparation. R. Gómez-Huelgas: concept and design, analysis and interpretation of data, and manuscript preparation. L.M. Pérez-Belmonte: concept and design, acquisition of participants and data, analysis and interpretation of data, and manuscript preparation. All authors have participated in drafting the manuscript and have read and approved the final version of the manuscript. M.A. Pérez-Velasco and A. Trenas contributed equally to this work and share first authorship.

CONFLICTS OF INTEREST

None.

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Available online 16 January 2024

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https://doi.org/10.1016/j.rec.2023.12.008

Heritable pulmonary arterial hypertension in rats with spontaneous systemic hypertension

Hipertensión arterial pulmonar hereditaria en ratas espontáneamente hipertensas

To the Editor,

An understanding of the health status of animals is essential to carry out research protocols correctly. The use of genetically defined strains of rodents is widespread, and a vast number of scientific studies use consanguineous lines to prevent genetic variability. The aim of this letter is to describe a relevant finding observed in one of these lines.

Heritable pulmonary arterial hypertension (PAH) falls under group 1 of the World Health Organization classification of pulmonary hypertension (PH), along with idiopathic PAH, PAH associated with connective tissue disease, and PAH related to disorders such as drug use (methamphetamines), congenital heart disease, cirrhosis of the liver, etc. This group also includes pulmonary veno-occlusive disease of autosomal recessive inheritance pattern.[1]

Heritable PAH is characterized by wall thickening of the pulmonary arterioles.[2] The cause is a genetic abnormality of autosomal dominant inheritance and sex-dependent incomplete penetrance with variable expression affecting 2 or more members of the same family. It is associated with a variety of mutations and is considered a serious condition that leads to right heart failure.[3]

Spontaneously hypertensive rats (SHR) belong to a consanguineous line developed in Japan in 1963 and are widely used in systemic hypertension research.[4] Some publications associate SHR with group 2 PH, secondary to left-side heart issues. Anatomic changes have also been observed in the pulmonary veins of SHR.[5]

The Institute of Cellular Physiology of the National Autonomous University of Mexico acquired 34 SHR older than 20 weeks to participate in an ischemia-reperfusion protocol authorized by the ethics committee. The inclusion criteria required the performance of a transthoracic echocardiogram.

The SHR were anesthetized with ketamine (40 mg/kg) and xylazine (5 mg/kg), the thorax was then shaved, and conventional echocardiographic slices were acquired with a Philips CX50 ultrasound machine (Koninklijke Philips N.V., Netherlands) using high-frequency transducers (L12-4 and S12-4). As an incidental finding, 6 SHRs (17.64%) exhibited evidence of chronic PH compared with the controls: decreased ratio between the right ventricle (RV) and the left ventricle (LV) (1.04 ± 0.12 vs 1.96 ± 0.25), RV dilatation (4.2 ± 0.21 vs 2.9 ± 0.28 mm), RV free wall hypertrophy (2.3 ± 0.29 vs 1.2 ± 0.15 mm), and leftward shift of the interventricular septum. The LV ejection fraction was $80.9\% \pm 0.9\%$ in the PAH group compared with $84.5\% \pm 4.4\%$ in the normal group.

These findings were confirmed in tissues from 2 siblings belonging to the same litter who showed signs of PH; the tissues were fixed in formalin, embedded in paraffin, sliced at a thickness of 4 μ, and stained with hematoxylin–eosin. Histology revealed

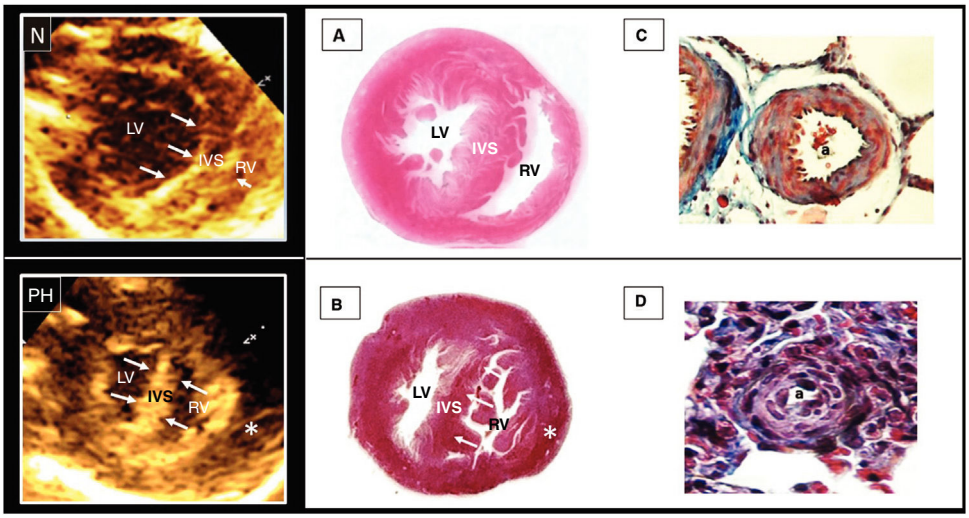

Figure 1. The left side shows 2 echocardiographic phenotypes: N, normal heart with preserved LV/RV ratio and rightward shift of the interventricular septum (pressure forces indicated by arrows) and PH, heart with RV free wall hypertrophy (*), equalized LV/RV ratio, and leftward shift of the interventricular septum. The right side shows anatomic pathology slices corresponding to a normal heart (A) and a heart with PH (B). B shows hypertrabeculation and RV hypertrophy with rectification of the interventricular septum. C shows a pulmonary arteriole with a normal lumen (a) and a wall formed by 2 or 3 layers of smooth muscle cells. D shows smooth cell proliferation with wall thickening and a reduced lumen (a). Masson trichrome stain, ×40. IVS, interventricular septum; LV, left ventricle; PH, pulmonary hypertension; RV, right ventricle.