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RESEARCH ARTICLE

Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)—a multicentre, double-blind, randomised, placebo-controlled trial

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Aims To determine the effect of the glucagon-like peptide-1 analogue liraglutide on left ventricular function in chronic heart failure patients with and without type 2 diabetes.

Methods and results LIVE was an investigator-initiated, randomised, double-blinded, placebo-controlled multicentre trial. Patients ($n = 241$) with reduced left ventricular ejection fraction (LVEF ≤45%) were recruited (February 2012 to August 2015). Patients were clinically stable and on optimal heart failure treatment. Intervention was liraglutide 1.8 mg once daily or matching placebo for 24 weeks. The LVEF was similar at baseline in the liraglutide and the placebo group (33.7 ± 7.6% vs. 35.4 ± 9.4%). Change in LVEF did not differ between the liraglutide and the placebo group; mean difference (95% confidence interval) was −0.8% (−2.1, 0.5; $P = 0.24$). Heart rate increased with liraglutide [mean difference: 7 b.p.m. (5, 9), $P < 0.0001$]. Serious cardiac events were seen in 12 (10%) patients treated with liraglutide compared with 3 (3%) patients in the placebo group ($P = 0.04$).

Conclusion Liraglutide did not affect left ventricular systolic function compared with placebo in stable chronic heart failure patients with and without diabetes. Treatment with liraglutide was associated with an increase in heart rate and more serious cardiac adverse events, and this raises some concern with respect to the use of liraglutide in patients with chronic heart failure and reduced left ventricular function. More data on the safety of liraglutide in different subgroups of heart failure patients are needed.

Keywords Glucagon-like peptide-1 • Liraglutide • Type 2 diabetes • Heart failure • Left ventricular function • Heart rate

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Introduction

In patients with chronic heart failure (CHF) and reduced left ventricular ejection fraction (LVEF), angiotensin-converting enzyme inhibitors, beta-blockers, and spironolactone reduce mortality and improve LVEF.[1–3] However, long-term survival and quality of life remain markedly impaired, especially in patients with diabetes.[4] We therefore need new, safe treatment modalities that can improve CHF symptoms and survival.

Glucagon-like peptide-1 (GLP-1) is a hormone secreted from the small intestine in response to food intake as part of the incretin system. It stimulates insulin production and inhibits glucagon excretion and thereby reduces blood glucose.[5] Native GLP-1 and GLP-1 analogues are also reported to have beneficial cardiovascular properties with effects on myocardial metabolism, nitric oxide production, afterload, and cardiac contractility.[6] A favourable effect on recovery of left ventricular function has recently been demonstrated in patients with ST-segment elevation myocardial infarction (STEMI) treated acutely with the GLP-1 analogue liraglutide.[7] Similar results were shown in patients with non-STEMI.[8] In addition, short-term clinical studies in small CHF populations have shown clinically relevant LVEF improvement with native GLP-1 in patients both with and without diabetes.[9] However, the only double-blinded and randomised study investigating the effect of 48-h GLP-1 treatment failed to demonstrate improvement in left ventricular function.[10]

The GLP-1 analogue liraglutide may have beneficial cardiovascular effects in CHF patients, but long-term randomised data on efficacy and safety are lacking. The present study investigates the effects of 24-week treatment with liraglutide vs. placebo on left ventricular function in stable CHF patients with reduced LVEF with and without type 2 diabetes.

Methods

The LIVE study was a 24-week investigator-initiated, randomised, double-blinded, placebo-controlled multicentre trial. The study was performed at four Danish Centres. Its design has been published elsewhere.[11]

Patients were recruited from diabetes and heart failure clinics. Patients who met the inclusion criteria and none of the exclusion criteria at pre-screening were invited for echocardiographic screening. Eligible patients were aged 30–85 years with CHF, had an LVEF ≤ 45% and were in New York Heart Association (NYHA) functional class I–III. Both patients with and without type 2 diabetes were recruited. All patients had been on stable, optimal pharmacological treatment for heart failure according to the European Society of Cardiology (ESC) guidelines for a minimum of 3 months before randomization.[12] If indicated, patients had a biventricular pacemaker implanted a minimum of 3 months before randomization.[13] A full list of inclusion and exclusion criteria is included in the Supplementary material online, *Table S1*.

All patients gave written informed consent and the study was performed in accordance with the Helsinki Declaration and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)–Good Clinical Practice (GCP) guidelines. Approval was obtained from the Scientific Ethics Committee in the Central Denmark Region, the Danish Medicines Agency, and the Data Monitoring Board. The study was registered on clinicaltrials.gov (identifier: NCT01472640) and monitored by the national GCP units. The statistical analysis plan was published on http://www.clinicaltrials.gov.

Patients were randomly assigned (1:1) to subcutaneous injectable liraglutide 1.8 mg once daily or matching placebo. Study medication was introduced at a dose of 0.6 mg/day, which was increased to 1.2 mg/day after 1 week and to 1.8 mg/day thereafter. A dose increase could be postponed depending on the patient's tolerance to the trial product or reduced at any time during the trial if required. Patients were assessed in detail at baseline, week 3, week 12, and at the end of the study. All visits included physical examination, adverse event assessment, and safety blood tests. Additional procedures performed at randomization and at the last visit included echocardiography, a 6-min walk test (6MWT), the Minnesota Living with Heart Failure questionnaire (MLHFQ), and collection of biosamples for a biobank. An outline of trial visits and examinations have been published elsewhere.[11]

Data on adverse events were collected and recorded at each contact. A senior specialist validated data on suspected cardiac-related events with a focus on aetiology, causality, and expectedness. An unblinded safety monitoring committee comprising independent cardiologists and endocrinologists evaluated data on serious adverse events and the study patients' safety.

Echocardiography

A screening echocardiography confirmed an acceptable apical acoustic window and LVEF ≤45%. Examinations were performed using a Vivid 9 scanner (version BT12; GE Vingmed Ultrasound, Horten, Norway). Two-dimensional and three-dimensional echocardiography were performed according to international scientific recommendations.[14] Left ventricular opacification was enhanced using the commercially available ultrasound contrast agent SonoVue (Bracco, Initios Medical AB, Copenhagen, Denmark). All images were stored digitally for subsequent analysis. To minimize variability all analysis were performed by one experienced echo technician blinded to treatment.[11]

Concomitant medication

The investigators were encouraged to continuously manage the patients' diabetes and cardiovascular risk. Adjustments were based on an algorithm described in a standard operating procedure. Patients with type 2 diabetes continued glucose-lowering therapy, but insulin and sulfonylurea doses were initially reduced to avoid hypoglycaemia and they were subsequently adjusted according to glucose measurements. Recurrent hypoglycaemia was followed by a reduction in non-investigational glucose-lowering agents before any reduction of the study drug. In cases of hypotension, diuretics and the investigational product were adjusted before heart failure treatment.

Outcomes

The primary outcome measure was change in LVEF from randomization to end of follow-up, as determined by three-dimensional contrast-enhanced echocardiography.

The secondary outcome measures included change in: peak systolic longitudinal tissue velocity (s′max), global longitudinal strain, left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), diastolic function, functional capacity measured by the 6MWT, plasma *N*-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, blood pressure, quality of life, and adverse events.

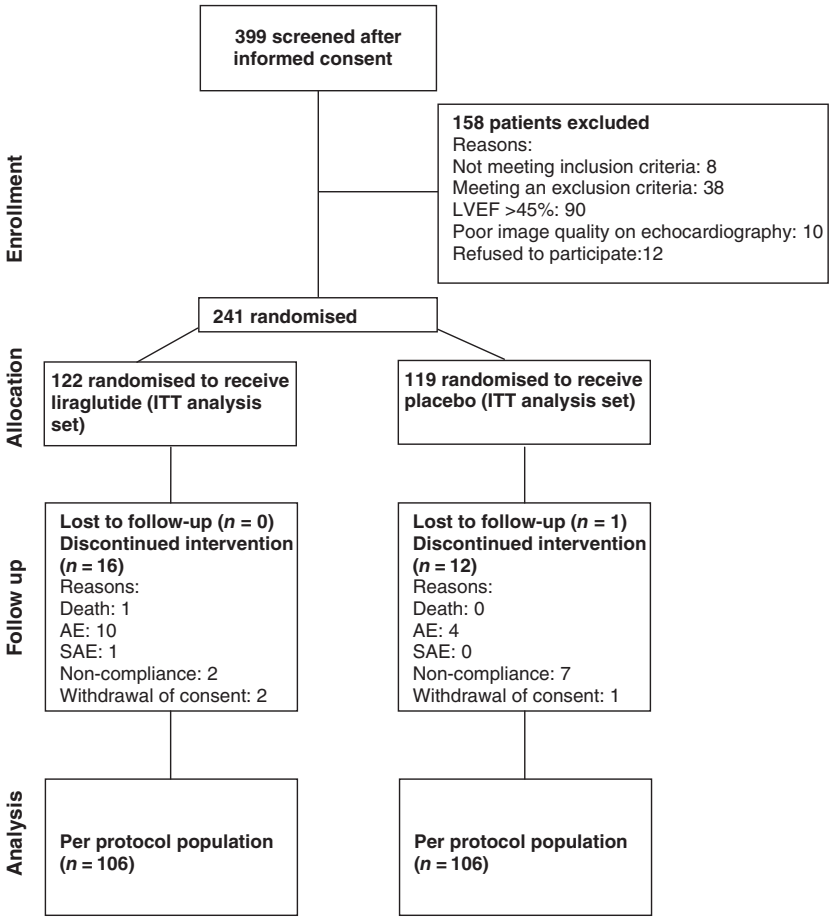

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram. AE, adverse events; ITT, intention to treat; LVEF, left ventricular ejection fraction; SAE, serious adverse events.

Statistical analysis

A sample size of 192 patients was estimated to provide 90% power for the primary endpoint with a 5% two-sided significance level. The study was designed to randomize 240 patients with an expected 20% dropout rate. The power analysis was based on a 6% standard deviation (SD) in LVEF (absolute units).[15] The estimated absolute LVEF change of 2.5% between the two treatment groups was based on clinical relevance, as determined from studies on the impact of angiotensin-converting enzyme inhibitors and beta-blockers on LVEF.[16,17]

Multiple imputation methods were applied to handle missing primary endpoint data (LVEF change). A total of 29 patients dropped out, and six of these patients had complete echocardiographic data. In the remaining 23 patients, baseline echocardiographic data were used for statistical imputation based on linear regression in STATA. A per protocol analysis was also performed. The per protocol population consisted of patients who completed the study with a valid baseline and 24-week assessment of LVEF and no major protocol deviations.

Data were analysed as the difference from baseline to follow-up. Variables are presented as mean ± SD, median [range], and number (percentage), as appropriate. Mean differences in change from baseline to follow-up between groups are presented with 95% confidence intervals (CIs). Normal distributed data were compared using the unpaired *t*-test or ANOVA, and Mann–Whitney *U*-test was used for non-normally distributed data. Chi-square and Fisher's exact tests were used to compare categorical variables. Multiple linear regression was used to analyse the relations between the primary outcome and treatment adjusted for baseline patient characteristics [age, diabetes, body mass index (BMI), LVEF, ischaemic heart disease, and estimated glomerular filtration rate (eGFR)]. Subgroup analyses were prespecified with respect to: presence of type 2 diabetes and cause of heart failure (ischaemic/non-ischaemic). Data were analysed according to treatment group A and B, and only unblinded after analyses were approved by the Steering Committee. Two-sided *P*-values <0.05 were considered statistically significant. No adjustments for multiple comparisons were performed. All calculations were performed using STATA, version 14.0 (College Station, TX, USA), a commercially available program.

Results

Patients were recruited between 1 February 2012 and 31 August 2015. In total, 399 patients gave informed consent and 241 patients fulfilled all entry criteria and were randomised to receive double-blind medication (liraglutide $n = 122$; placebo $n = 119$) (*Figure 1*). Of the 241 patients randomised, 29 (12%) dropped out

Table 1 Baseline clinical and laboratory characteristics in 241 patients with chronic heart failure

Characteristics	Liraglutide ($n = 122$)	Placebo ($n = 119$)
General		
Sex, male/female	109/13	106/13
Age, years	65 (9.2)	65 (10.7)
BMI, kg/m^2	28.0 (3.8)	29.8 (4.6)
Type 2 diabetes, *n* (%)	39 (32)	35 (29)
Smoking (current), *n* (%)	25 (21)	23 (19)
Ischaemic heart disease, *n* (%)	72 (59)	73 (62)
Atrial fibrillation, *n* (%)	34 (28)	34 (29)
6MWT, m	453 ± (104)	441 (122)
Clinical/laboratory		
Systolic BP, mmHg	128 (20)	127 (18)
Diastolic BP, mmHg	77 (11)	76 (11)
Heart rate, b.p.m.	67 (10)	67 (11)
HbA1c, %, mmol/mol	5.9 (0.7)	6.0 (0.8)
	41.2 (7.5)	42.6 (8.7)
eGFR, mL/min.1.73 m^2	79 (20)	80 (21)
Plasma NT-proBNP, pg/mL	413 (208–926)	388 (153–880)
NYHA class		
I, *n* (%)	36 (31)	35 (30)
II, *n* (%)	65 (55)	64 (56)
III, *n* (%)	17 (14)	16 (14)

Data are mean (SD), *n* (%) or median (IQR).
BMI, body mass index; 6MWT, 6-min walk test; BP, blood pressure; eGFR, estimated glomerular filtration rate; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Table 2 Baseline echocardiographic data in 241 patients with chronic heart failure

Parameter	Liraglutide ($n = 122$)	Placebo ($n = 119$)
Systolic function		
LVEF, %	33.7 (7.6)	35.4 (9.4)
Global longitudinal strain, %	−11.3 (2.9)	−11.3 (3.5)
s′max, cm/s	3.8 (1.2)	3.8 (1.3)
LVESV, mL	111 (60)	109 (78)
LVEDV, mL	163 (71)	165 (111)
Diastolic function		
E-wave, cm/s	73 (30)	71 (27)
A-wave, cm/s	59 (28)	61 (26)
E-deceleration, ms	156 (42)	158 (34)
IVRT, ms	80 (17)	87 (39)
Atrial volume, mL	84 (28)	79 (32)
e′ (average), cm/s	6.6 (2.1)	6.9 (2.4)
E/e′ ratio	12.6 (6.0)	11.7 (5.5)

Data are mean (SD).
LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; IVRT, isovolumetric relaxation time.

during the treatment period (*Figure 1*). The number of dropouts did not differ significantly between treatment groups. In the liraglutide group, dropout was caused mainly by gastrointestinal adverse events, predominantly during study drug titration within the first weeks after randomization.

The demographic characteristics of the intention-to-treat population are summarized in *Table 1*. The treatment groups were well balanced with respect to NYHA classification, duration of heart failure, atrial fibrillation, ischaemic heart disease, diabetes status, glycaemic control, blood pressure, hypertension, heart rate, kidney function, and NT-proBNP. Body mass index was lower in the liraglutide group ($P < 0.0001$). Baseline echo parameters were similar in the two treatment groups (*Table 2*). The mean LVEF was 33.7 ± 7.6% in the liraglutide group and 35.4 ± 9.4% in the placebo group ($P = 0.13$).

All patients were on optimal treatment for heart failure. In both groups more than 91% ($n = 221$) received beta blockade and 97% ($n = 233$) received renin–angiotensin system inhibition. Most patients with diabetes were treated with metformin ($n = 52$, 70%). Medications did not differ between groups (see the Supplementary material online, *Table S2*). Compliance with the investigational medicine product was estimated from drug accountability to be 90% with no difference between groups. At the end of the study period, the average liraglutide dose was 1.4 mg (1.3, 1.5) and the average placebo dose was 1.6 mg (1.5, 1.7) ($P = 0.0005$).

The change in LVEF from baseline to week 24 was not significantly different between treatment groups. The mean absolute increase in LVEF was 0.7 ± 5.4% during treatment with liraglutide and 1.5 ± 5.0% in the placebo group, and did not differ between treatment groups [mean difference −0.8% (−2.1, 0.5), $P = 0.24$)] (*Figure 2*). The per protocol population did not differ from the intention-to-treat population with respect to age, LVEF, diabetes, or kidney function. The absolute increase in LVEF was 0.8 ± 4.7% in the liraglutide group and 1.7 ± 4.4% in the placebo group [mean difference −0.9% (−2.1, 0.3), $P = 0.15$]. Multiple linear regression was used to analyse the relation between the primary outcome and treatment adjusted for baseline patient characteristics (age, diabetes, BMI, LVEF, ischaemic heart disease, and eGFR). This analysis did not change the overall conclusion. There was no interaction with diabetes status for the primary endpoint ($P = 0.59$).

We observed no significant differences in changes in global longitudinal strain, s′max, LVESV, or LVEDV between groups (*Table 3*). The atrial volume decreased significantly in the liraglutide group compared with the placebo group [mean difference −8.7 mL (−14.2, −3.2), $P = 0.002$]. Furthermore, a small decrease in E/e′ ratio in the liraglutide group compared with the placebo group [mean difference −1.4 (−2.7, −0.1), $P = 0.03$] was seen. The E-wave and E-deceleration time also tended to be reduced with liraglutide treatment, whereas no between-group differences were observed for A-wave, isovolumetric relaxation time, left atrial volume index, and e′ (average) (*Table 3*).

At the end of treatment, patients in the liraglutide group were able to walk 28 ± 65 m longer in a 6MWT compared with 3 ± 89 m in the placebo group [mean difference 24 m (2, 47), $P = 0.04$]. The NYHA functional class did not change during treatment in the

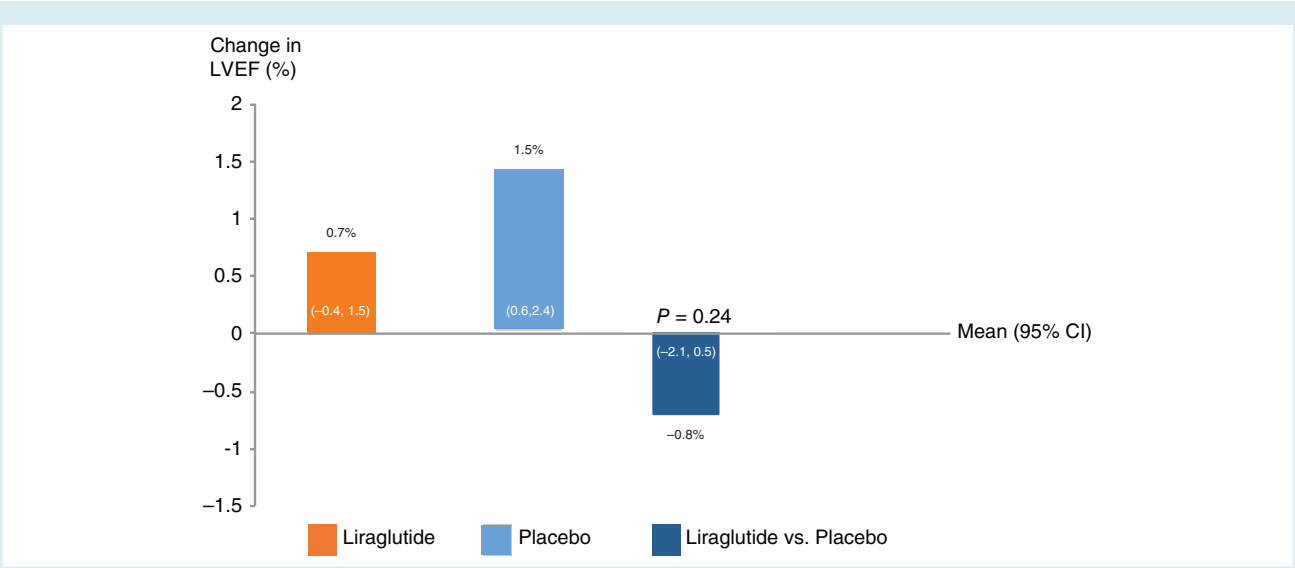

Figure 2 Change in primary endpoint. CI, confidence interval; LVEF, left ventricular ejection fraction.

majority of patients. Improvement ($n = 34$, 16%) and worsening ($n = 29$, 14%) of NYHA functional class occurred in a similar number of patients in the two treatment groups. Liraglutide treatment was associated with a weight loss of 2.2 ± 3.1 kg whereas there was no change in the placebo group (0.0 ± 3.0 kg) [mean difference −2.2 (−3.0, −1.4), $P < 0.0001$]. Although systolic blood pressure was reduced in the liraglutide group, there was no statistically significant difference between the groups. In contrast, an increase in heart rate averaging 6 ± 9 b.p.m. in the liraglutide group and a decrease of 1 ± 8 b.p.m. in the placebo group (mean difference 7 b.p.m. (5, 9), $P < 0.0001$) were seen (*Table 3*). Quality of life improved similarly in both treatment groups during treatment [mean difference −1.6 (−5.3, 2.0), $P = 0.39$].

Plasma NT-proBNP did not change significantly in either group during treatment; neither were there any differences observed between groups [mean difference −140 pg/mL (−317, 37), $P = 0.12$]. In all patients, after 24 weeks of treatment, glycated haemoglobin (HbA_{1c}) was reduced in the liraglutide group compared with the placebo group [mean difference −0.4% (−0.5, −0.3), $P < 0.0001$].

More patients experienced serious cardiac adverse events ($n = 12$, 10%) in the liraglutide group than in the placebo group ($n = 3$, 3%), ($P = 0.04$). The events comprised one death caused by ventricular tachycardia (VT), non-fatal VT, atrial fibrillation requiring intervention, aggravation of ischaemic heart disease, and one case of worsening of heart failure (*Table 4*). The patient with a fatal event had VT shortly after titration to the maximal dose of the drug being investigated, treatment was immediately stopped. The patient died 17 days after treatment was discontinued. All other serious cardiac events occurred in patients on study drug but no relationship with duration of treatment was observed. The group of patients experiencing a serious cardiac adverse event did not differ from the rest of the population with respect to age, diabetes status, BMI, hypoglycaemic events, LVEF, NYHA class, atrial fibrillation, heart rate at baseline, change in heart rate, beta-blocker treatment, or eGFR. Significantly more events were seen in the group treated with liraglutide [hazard ratio (HR) 3.9, 95% CI 1.1, 13.8; log rank $P = 0.029$]. Non-serious cardiac adverse events occurred in 13 patients (11%) in the liraglutide group vs. 9 patients (8%) in the placebo group ($P = 0.14$). These events comprised non-sustained VT, supraventricular tachycardia, atrial fibrillation, and worsening of heart failure. In patients with diabetes, no VT events were recorded, two patients had atrial fibrillation requiring intervention (5%), and two patients had aggravation of existing ischaemic heart disease (5%) in the liraglutide group compared with none in the placebo group.

Non-serious gastrointestinal side-effects, especially nausea and constipation, were more frequent in the liraglutide group ($n = 80$, 66%) than in the placebo group ($n = 19$, 16%; $P < 0.0001$) (see the Supplementary material online, *Table S3*). Central nervous system-classified events, especially dizziness, were seen more often in the liraglutide group ($n = 38$, 31% vs. $n = 15$, 13%; $P = 0.002$). Hypoglycaemia occurred in four patients (10%) with diabetes treated with liraglutide and in three patients (9%) with diabetes receiving placebo ($P = 0.73$). All the events were mild and documented by self-measured blood glucose.

Patients with and without diabetes did not differ in treatment responses; neither did the treatment effect differ from the overall result in patients with and without ischaemic heart disease, patients tolerating full doses, and patients with hypertension, atrial fibrillation, or long duration of heart failure. Results for patients with diabetes are shown in the Supplementary material online, *Table S4*.

Discussion

Liraglutide treatment for 24 weeks did not improve LVEF or other systolic function measures compared with placebo in patients

Table 3 Change in left ventricular function and clinical and laboratory characteristics from baseline to end of study in 241 patients with chronic heart failure

	Liraglutide ($n = 122$)	Placebo ($n = 119$)	Delta estimates (95% CI)	*P*-value
Change in echocardiographic data				
Systolic function				
LVEF, %	0.7 (5.4)	1.5 (5.0)*	−0.8 (−2.1, 0.5)	0.24
Global longitudinal strain, %	0.6 (2.2)*	0.1 (1.8)	0.5 (−0.1, 1.1)	0.13
s′max, cm/s	−0.03 (1.2)	0.17 (1.8)	−0.2 (−0.6, 0.2)	0.28
LVESV, mL	2.3 (17)	−0.3 (9)	2.6 (−1.2, 6.4)	0.19
LVEDV, mL	3.4 (25)	0.0 (15)	3.4 (−2.3, 9.2)	0.24
Diastolic function				
E-wave, cm/s	−4.5 (17)*	−0.3 (14)	−4.2 (−8.5, 0.1)	0.056
A-wave, cm/s	2.5 (25)	0.3 (16)	2.2 (−3.7, 8.1)	0.46
E-deceleration, ms	−12.4 (44)*	2.4 (36)	−10.0 (−21.2, 1.2)	0.08
IVRT, ms	−0.2 (11)	−8.1 (45)	7.9 (−9.7, 25.5)	0.37
Atrial volume, mL	−5.0 (18)*	3.7 (18)	−8.7 (−14.2, −3.2)	0.002
e′ (average), cm/s	0.01 (1.4)	−0.05 (1.6)	0.1 (−0.4, 0.5)	0.81
E/e′ ratio	−0.7 (4.6)	0.7 (4.3)	−1.4 (−2.7, −0.1)	0.03
Change in clinical and laboratory data				
6MWT, m, median (IQR)	28 (65)*	3 (89)	24 (2, 47)	0.04
MLHFQ, grade	−2.7 (12)	−1.1 (15)	−1.6 (−5.3, 2.0)	0.39
Systolic BP, mmHg	−4 (12)*	−2 (16)	−2 (−6, 3)	0.45
Diastolic BP, mmHg	−1 (10)	−1 (9)	−0.2 (−3, 2)	0.89
Heart rate, b.p.m.	6 (9)*	−1 (8)	7 (5, 9)	<0.0001
BMI	−0.7 (1.0)	0.1 (1.1)	−0.8 (−1.1, −0.4)	<0.0001
HbA_{1c}, %, mmol/mol	−0.3 (0.6)* −2.9 (6.2)*	0.1 (0.5)* 1.5 (5.3)	−0.4 (−0.5, −0.3) −4.4 (−6, −3)	<0.0001
eGFR, mL/min.1.73 m^2	−0.5 (10)	0.6 (10)	−1.1 (−3.8, 1.5)	0.40
Plasma NT-proBNP, pg/mL	−62 (735)	78 (524)	−140 (−317, 37)	0.12

Imputation strategy was used for the primary end-point LVEF. Data are mean (SD) or mean (95% CI).
CI, confidence interval; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; IVRT, isovolumetric relaxation time; 6MWT, 6-min walk test; MLHFQ, Minnesota Living with Heart Failure Questionnaire; BP, blood pressure; BMI, body mass index; HbA_{1c}, glycated haemoglobin; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide.
*End of treatment vs. baseline $P \leq 0.05$.

with stable CHF. It did, however, reduce HbA_{1c} and body weight. Liraglutide was also associated with a clinically significant 6 b.p.m. increase in heart rate, and more patients experienced serious cardiac events in the liraglutide group than in the placebo group.

Dipeptidyl peptidase 4 (DPP-4) inhibitors act through inhibition of GLP-1 degradation and inhibitors have been associated with an increased risk of heart failure.[18] Furthermore, in a study of patients with reduced LV function, vildagliptin increased LVEDV, and no significant effect on LVEF was observed.[19] In contrast, a very recent large observational study of incretin-based therapies and heart failure has been published, and did not find increased risk of hospitalization for heart failure.[20]

Previous small and short-term data on the effect of GLP-1 on LVEF in CHF have been promising. The LIVE study examined the effect of liraglutide on left ventricular function in patients with CHF and reduced LVEF.[11] Although reduction in HbA_{1c} and body weight may theoretically improve myocardial metabolism and function, the LIVE study showed no significant improvement in systolic function after 24 weeks of liraglutide treatment. It can be argued that inclusion of non-diabetic patients with less pronounced metabolic derangement reduced the potential effect of liraglutide treatment on myocardial metabolism. However, a subgroup analysis of the patients with type 2 diabetes suggested no beneficial effects on cardiac function either. Furthermore, the present result in patients with longstanding heart failure is in accordance with data from the FIGHT study investigating the effect of liraglutide in acute heart failure, which also failed to demonstrate a beneficial effect on left ventricular function. Furthermore, a trend for harm assessed by death and hospitalization owing to heart failure was observed.[21]

Data from the LEADER trial investigating the impact of liraglutide on cardiovascular outcomes were recently published.[22] LEADER included patients with diabetes and a history of any major cardiovascular disease event or high risk of such. At enrolment 17% of the LEADER population had a history of heart failure. Liraglutide reduced the primary composite cardiovascular endpoint and death from cardiovascular and all-causes. Despite this, liraglutide did not decrease hospitalization for heart failure.[22] Importantly, no data on LVEF is available in LEADER and thus, the prevalence of heart failure patients with reduced ejection fraction is unknown. The effect of liraglutide in heart failure patients with reduced and preserved ejection fraction may potentially differ. Furthermore, only patients with diabetes were included in LEADER.

Table 4 Serious adverse events in 241 patients with chronic heart failure presented according to body system

	Liraglutide *n* (%)	Placebo *n* (%)
Cardiac		
Death due to ventricular tachycardia	1	0
Ventricular tachycardia	3	1
Atrial fibrillation (DC-converted)	4	2
Acute coronary syndrome	3	0
Worsening of CHF	1	0
Subtotal	12 (10)*	3 (3)
Gastrointestinal		
Gastritis	0	1
Subtotal	0	1 (1)
Central nervous system		
Apoplexy	1	2
TCI	1	0
Dizziness	0	1
Subtotal	2 (2)	3 (3)
Other		
Infections	5	4
Vascular (orthostatic hypotension)	4	0
Tendinitis/tenectomy	1	1
Reduced kidney function	0	1
Urothelial neoplasm	1	0
Anaemia	1	0
Pruritus	0	1
Pacemaker electrode procedures	1	2
Subtotal	13 (11)	9 (8)

DC, direct current; CHF, chronic heart failure; TCI, transient cerebral ischaemia.
*$P \leq 0.05$ vs. placebo

An increase in heart rate of 2–3 b.p.m. is a well-known side-effect of liraglutide in patients without heart failure.[23] In the present study, liraglutide was associated with an even more pronounced increase in heart rate of 6 b.p.m. One recent study investigating heart rate with Holter electrocardiography reported a pronounced average increase of 13 b.p.m.[24] It is unlikely that the increased heart rate is caused by liraglutide-induced volume depletion as the weight reduction with liraglutide is presumably caused by loss of adipose tissue.[25] In addition, patients in the liraglutide group in the current study did not achieve a significantly lower blood pressure or higher haematocrit. The effect on heart rate may be mediated through direct stimulation of GLP-1 receptors in the sinoatrial node.[26] Interestingly, a recent study demonstrated that GLP-1 regulates HL-1 atrial myocyte arrhythmogenesis through modulating calcium-handling proteins.[27] Notably, the effect on heart rate in the LIVE study was observed despite concomitant treatment with maximum tolerable beta-blocker dose. On average, the dose was 74% of the target beta-blocker dose, which is similar to the dose reached in other CHF trials (i.e. the COMET Trial).[28] The observed increase in heart rate is a matter of concern as an elevated resting heart rate, even if moderate, is a negative prognostic indicator in heart failure.[29,30] The risk for cardiovascular complications in CHF increases progressively when heart rate exceeds 70 b.p.m.[31] Therefore, heart rate changes in the present study may have caused the lack of improvement in the patients treated with liraglutide.

In a subgroup analysis of the effect of liraglutide and placebo in patients with diabetes, no difference with regard to changes in LVEF was observed between groups. Liraglutide reduced body weight and HbA_{1c}. Heart rate was increased and no differences between groups were observed in walking distance or NT-proBNP levels. No statistical significant difference between groups was observed for adverse cardiac events or hospitalizations for heart failure in patients with diabetes. These data should, however, be interpreted with caution, since the study was not powered for this subgroup analysis.

Limitations of the study

The variability in LVEF estimated by echocardiography may have produced a type 2 error causing us to overlook minor differences in LVEF. This risk, however, is minimal, as the recruitment goal was reached and our final analysis showed a narrow 95% CI for the difference in LVEF between treatment arms. Moreover, no other echocardiographic parameter showed signs of improvement in systolic function. Some of the diastolic parameters improved, but the clinical significance of these findings is unclear.

Patients were treated with liraglutide for 24 weeks, but the treatment time may have been too short to induce cardiac remodelling and left ventricular function improvements. On the other hand, treatment with an angiotensin-converting enzyme inhibitor, or a beta-blocker induces cardiac remodelling after approximately 3 months.[16,17]

Finally, only 11% of the present patient group were women, and thus the observed effects of liraglutide may not be representative for women with heart failure. The present study does not have sufficient power for a subgroup analysis to explore this further. However, 36% of the patients in the LEADER trial were women, and the interaction term for the primary outcome including cardiovascular death, non-fatal myocardial infarction or non-fatal stroke was not statistically significant.[22]

Conclusion

Liraglutide did not affect left ventricular systolic function compared with placebo in stable CHF patients with and without diabetes. Liraglutide resulted in weight loss, improved glycaemic control, and an improvement in physical performance. Treatment with liraglutide was also associated with a 6 b.p.m. increase in heart rate and more serious cardiac adverse events. Although the latter effects were not the primary endpoint of the LIVE study, our findings raise some concern with respect to the use of liraglutide in patients with CHF and reduced left ventricular function. However, it is uncertain whether the results are representative for other heart failure populations including patients with preserved ejection fraction or diastolic dysfunction. More data on the safety of liraglutide in different subgroups of heart failure patients are needed.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Inclusion and exclusion criteria.

Table S2. Baseline treatment for heart disease and diabetes.

Table S3. Non-serious adverse events.

Table S4. Change in echocardiographic, clinical, and laboratory characteristics in patients with diabetes.

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