Effect of liraglutide on myocardial glucose uptake and blood flow in stable chronic heart failure patients: A double-blind, randomized, placebo-controlled LIVE sub-study

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Background. **The glucagon-like peptide-1 analog liraglutide increases heart rate and may be associated with more cardiac events in chronic heart failure (CHF) patients. We studied whether this could be ascribed to effects on myocardial glucose uptake (MGU), myocardial blood flow (MBF) and MBF reserve (MFR).**

Methods and Results. **CHF patients with left ventricular ejection fraction ≤45% and without type 2 diabetes were randomized to liraglutide (N = 18) 1.8 mg once daily or placebo (N = 18) for 24 weeks in a double-blinded design. Changes in MGU during an oral glucose tolerance test (OGTT) and changes in MBF and MFR from baseline to follow-up were measured quantitatively by ^{18}F-FDG and ^{15}O-H_2O positron emission tomography. Compared with placebo, liraglutide reduced weight ($P = 0.03$), HbA1c ($P = 0.03$) and the 2-hour glucose value during the OGTT ($P = 0.004$). Despite this, changes in MGU ($P = 0.98$), MBF ($P = 0.76$) and MFR ($P = 0.89$) from baseline to follow-up did not differ between groups. Furthermore, there was no association between the level of insulin resistance at baseline and changes in MGU in patients treated with liraglutide.**

Conclusion. **Liraglutide did not affect MGU, MBF, or MFR in non-diabetic CHF patients. Any potential increase in cardiac events in these patients seems not to involve changes in MGU,**

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MBF, or MFR.

Trial Registration. **Trial registry: http://www.ClinicalTrials.org. Identifier: NCT01472640. Url: https://clinicaltrials.gov/ct2/show/NCT01472640?term=NCT01472640&rank=1 (J Nucl Cardiol 2019;26:585–97.)**

Key Words: Heart failure • metabolism • nuclear cardiology and PET • echocardiography • clinical studies

Abbreviations	
CHF	Chronic heart failure
HEC	Hyperinsulinemic-euglycemic clamp
LVEF	Left ventricular ejection fraction
MGU	Myocardial glucose uptake
MBF	Myocardial blood flow
MFR	Myocardial flow reserve
OGTT	Oral glucose tolerance test
PTI	Perfusable tissue index
WMS	Wall motion score

INTRODUCTION

Liraglutide is a glucagon-like peptide-1 (GLP-1) agonist that increases insulin secretion and decreases glucagon release in response to hyperglycaemia. It is widely used as a glucose-lowering drug for treatment of type 2 diabetes (T2D).[1] In addition to their glucose-lowering effects, GLP-1 receptor agonists have been shown to protect the heart during acute ischemia[2] and to improve mitochondrial function,[2] microvascular function,[3] and myocardial glucose uptake (MGU) in experimental animal models of heart failure.[4] A similar increase in MGU was demonstrated in healthy men and patients with T2D,[5,6] whereas no effect was found in 11 heart failure (HF) patients after 12 weeks of treatment with the GLP-1 analog albiglutide by use of a hyperinsulinemic-euglycemic clamp (HEC).[7] The effect of GLP-1 receptor agonists on myocardial flow reserve (MFR) has been equivocal.[6,8-10]

The randomized clinical trials LIVE[11] and FIGHT[12] failed to show improvement in left ventricular ejection fraction (LVEF) by liraglutide treatment in patients with HF and reduced LVEF. Both studies demonstrated an increase in cardiovascular events. It remains unclear which mechanisms caused this concerning finding, which is in contrast to the LEADER trial that showed a significant reduction in the rate of all-cause mortality.[13] However, patients included in the LEADER trial had unknown LVEF, and only 16% had clinical signs of heart failure.

MGU[14] and MFR[15] are closely related to prognosis in HF patients, but neither MGU nor MFR were investigated in the LIVE, FIGHT or the LEADER studies. Hence, it remains unknown whether liraglutide affects myocardial perfusion and MGU in HF patients during daily life. Such investigations may uncover some of the potential beneficial effects and concerns regarding the use of GLP-1 analogs in HF patients with reduced LVEF.

We hypothesized that liraglutide treatment increases myocardial glucose uptake and improves MFR. The purpose of the present randomized, double-blind study was to examine the effect of 24 weeks of treatment with liraglutide vs placebo on MGU and MFR using quantitative positron emission tomography (PET) in HF patients.

METHODS

The present study is a sub-study of the clinical, randomized LIVE study which included 241 patients with chronic HF. The protocol for the LIVE study has been published.[16] The main inclusion criteria in the LIVE study were as follows: (1) stable chronic heart failure (CHF) and optimal pharmacological treatment for at least 3 months before randomization; (2) LVEF of 45% or lower; and (3) New York Heart Association (NYHA) class I-III. Patients were randomized to receive either liraglutide (1.8 mg/day) or placebo for 24 weeks in a double-blinded design.

Patients randomized into the LIVE study at Aarhus University Hospital, Denmark, were consecutively included. Patients included in the present study were required to be older than 50 years and not to have known T2D or HbA1c $\geq$6.5% ($\geq$48 mmol/mol), severe chronic obstructive pulmonary disease (defined as forced expiratory volume in 1 seconds (FEV1) <50%), or untreated 2nd or 3rd degree atrioventricular block.

Echocardiographic Measurements

EchoPAC 12 software (GE-Vingmed Ultrasound, Horten, Norway) was used for the analyses. LVEF was measured using the biplane-modified Simpson's method with ultrasound contrast (Sonovue®, Bracco, Initios Medical AB, Copenhagen, Denmark). Global strain was measured by two-dimensional (2D) speckle tracking. Echocardiographic wall motion score (WMS) was obtained using the scoring scale: normokinesia = 2, hypokinesia = 1, akinesia = 0, and dyskinesia = −1.[17]

Oral Glucose Tolerance Test (OGTT)

All patients were subjected to an OGTT by oral intake of 75 g glucose in a fasting state. Glucose levels were measured before and during the test. Impaired glucose tolerance (IGT)

was defined as p-glucose ≥7.8 mM 2 hours after glucose intake.

Myocardial Glucose Uptake (MGU)

MGU was quantified using dynamic 18-fluoro-D-glucose (FDG) PET/CT (GE Discovery 690 PET/CT). One hour after initiation of the OGTT, 18F-FDG was injected intravenously (administered activity 400 MBq) with simultaneous start of the dynamic PET scan. The scan lasted 70 minutes (37 frames: 1 × 10, 8 × 5, 4 × 10, 3 × 20, 5 × 30, 5 × 60, 4 × 150, 4 × 300, 3 × 600 seconds). Images were reconstructed using all relevant corrections (attenuation, scatter, dead time and randoms) using the VUEPoint HD SharpIR PSF-based reconstruction algorithm in a 3.27 × 3.27 × 3.27 mm matrix. We performed Gjedde-Patlak analysis[18] with an image-derived arterial input function automatically obtained using cluster analysis (Cardiac VUer software)[19] to obtain the 18F-FDG influx constant (K_i) from the relation:

$$\frac{C_i t}{C_p t} = K_i \frac{\int_0^t C_p \mathrm{d}t}{C_p(t)} + V_d,$$

where *Ci* is the myocardial 18F-FDG radioactivity and *Cp* is the plasma 18F-FDG radioactivity at time *t*. Plots of $C_i(t)/C_p(t)$ versus $C_p(t)\mathrm{d}t/C_p(t)$ were fitted from $T = 10$ to $T = 60$ minutes after 18F-FDG injection to straight lines by conventional least squares methods and the slopes of the best fits were taken as estimates of K_i.

The glucose levels (Cglu) during the FDG examination were averaged ($t = 0$ minutes, $t = 10$ minutes, $t = 30$ minutes, $t = 60$ minutes) and used to calculate MGU (MGU = Ki*Cglu/LC, where LC is the lumped constant and assumed not to differ between visits and therefore fixed at 1). Patients fasted for at least 10 hours before the FDG scan, but were allowed to consume water. Both global analysis and segmental (16-segment model) analysis were applied. Dysfunctional segments were characterized as viable or non-viable. Viable segments were defined as having ≥50% of maximal FDG uptake and non-viable segments as having <50% of maximal FDG uptake in each patient as previously described.[20]

Myocardial Blood Flow (MBF) and Myocardial Perfusion Reserve (MFR)

MBF was quantified at rest and during adenosine-induced hyperaemia (stress) using dynamic ^{15}O-H_2O PET/CT scans as described previously[21] and calculated using Cardiac VUer. In brief, the arterial and venous blood pool were segmented automatically and used to extract the arterial input function, which was then used to generate parametric images of MBF. Then, these parametric images were used for reorientation to short-axis images on which the left ventricle was then defined automatically and segmented. Activity administered was 400 MBq. Medications that may influence perfusion and/or response to adenosine were paused before the investigation (long-acting nitrates, caffeine-containing preparations/xanthines and dipyridamole).

We measured both global and regional perfusion (16-segment model). MFR was calculated as the ratio between adenosine-induced hyperaemia MBF and resting MBF. Perfusable tissue index (PTI) was calculated[22] to determine the fibrotic burden, and MBF was corrected for rate-pressure product (RPP)[23] as previously described.

Integrated Analysis

Myocardial segments were defined by a combination of WMS and FDG-PET examinations and grouped into those who had preserved function (WMS = 2), were dysfunctional but viable (WMS <2, normal FDG uptake) and those who were dysfunctional and non-viable (WMS <2, low FDG uptake).

Blood Samples

Insulin levels were analyzed from blood samples taken before the OGTT, after 60 and 120 minutes. The homeostasis model assessment-estimated insulin resistance (HOMA-IR) was calculated. Free fatty acids (FFA) were measured 120 minutes after the oral glucose load.

Statistics

For comparison between groups, Student's *t* test was used for normally distributed data, Wilcoxon rank sum test for skewed data and Fischer's exact test. Pearson's or Spearman's rank correlation test were used when appropriate. All data are presented as mean ± standard deviation (SD), median [25%; 75%], or mean ± standard error of mean (SEM) when appropriate. STATA 14 was used for statistical analysis.

In previous studies, the coefficient of variation (CV) for 15O-H2O PET was 15%.[24] With N = 36 and an expected drop-out of 20%, a significance level of 5% and a power of 80%, we would be able to detect differences of 15% between groups with regard to MBF.

Ethics

All patients gave informed consent, and the local Ethics Committee of the Central Denmark Region and the Danish Data Protection Agency approved the study. The study was a sub-study of the LIVE study registered at www.clinicaltrials.gov (NCT01472640).

RESULTS

Among 41 patients enrolled in the LIVE study and screened consecutively for eligibility for inclusion into the present study (Figure 1), 1 had asthma and 4 had T2D. In total, 36 HF patients were randomized (liraglutide, n = 18; placebo, n = 18). Their LVEF was 33 ± 8% without any difference between the study groups (Table 1). The two groups were well-balanced with regard to demographics, underlying condition of

HF, clinical/laboratory measurements of MGU, MBF at rest, MFR, and treatment for HF (Table 1). Two patients in each group discontinued treatment due to gastrointestinal side effects. One patient in the placebo group declined H_2O-PET at follow-up due to discomfort, whereas another patient that received liraglutide declined adenosine stress test during H_2O-PET at follow-up but accepted the resting H_2O-PET (Figure 1). On average, patients received 1.6 ± 0.5 mg of liraglutide per day.

Clinical and Laboratory Data

Compared with patients treated with placebo, patients treated with liraglutide reduced their weight ($P = 0.03$) and had increased heart rate ($P = 0.004$), whereas changes in blood pressure did not differ from baseline to follow-up between the groups (Table 2). While differences in fasting p-glucose did not differ between the groups, we observed a significantly larger reduction in HbA1c ($P = 0.03$) and the 2-hour plasma-glucose value during the OGTT ($P = 0.004$) in the liraglutide group than in the control group. Compared with placebo, liraglutide did not affect changes in insulin levels ($P = 0.93$, Figure 2B), HOMA-IR index ($P = 0.52$), or the 2-hour FFA levels (liraglutide: −0.78 ± 0.71 μmol/L, placebo: −1.90 ± 0.54 μmol/L, $P = 0.22$) following OGTT.

Outcome: Global Myocardial Measurements

A time-activity curve during rest and hyperemia is shown in Figure 3. Baseline MBF at rest was 0.77 ± 0.18 mL/g/minutes and MFR was 2.60 ± 1.12 without any effect of liraglutide on changes from baseline to follow-up between the groups (Table 3). PTI did not differ at baseline between the groups ($P = 0.69$), and liraglutide treatment had no effect on PTI ($P = 0.29$). Similarly, global MGU was 0.26 ± 0.02 μmol/g/minutes at baseline and there was no difference with regard to changes MGU between the

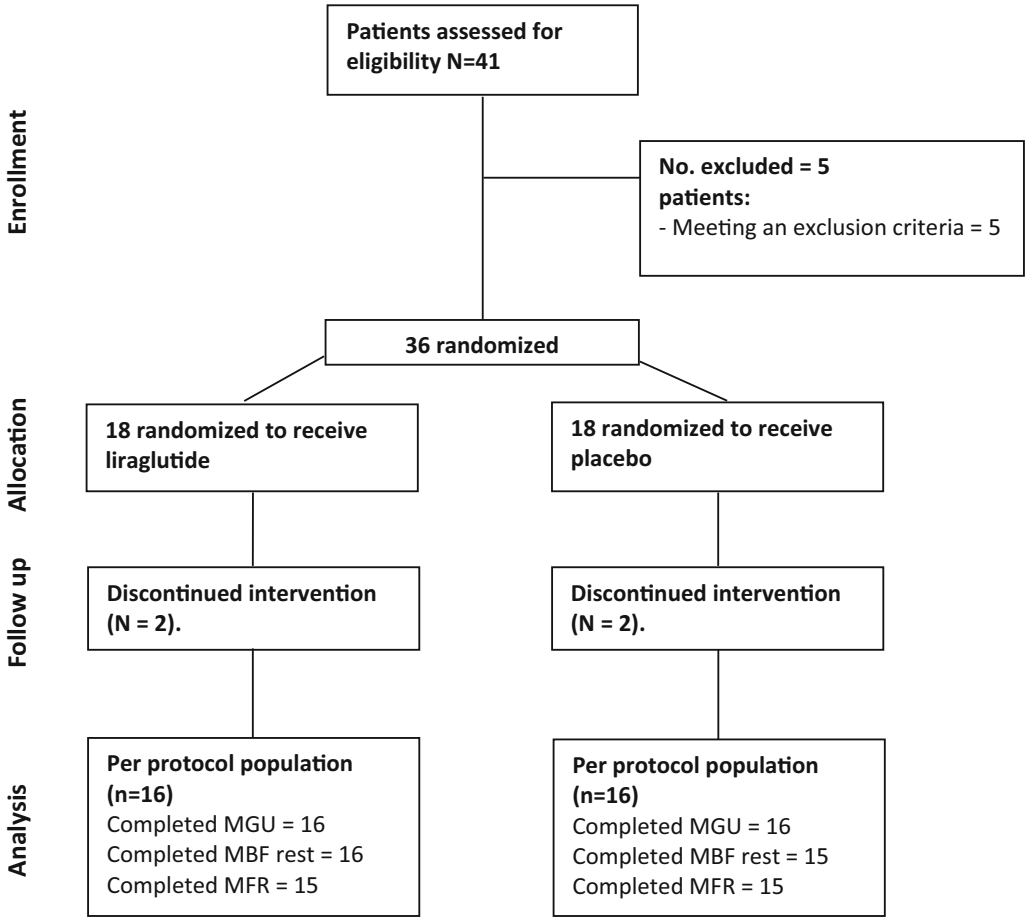

Figure 1. CONSORT diagram showing the flow of patients. *MGU*, myocardial glucose uptake; *MBF*, myocardial blood flow; *MFR*, myocardial flow reserve.

Table 1. Baseline clinical, laboratory and treatment characteristics of enrolled participants

Baseline clinical characteristics			
General	Liraglutide	Placebo	*P* value
Gender (male/female)	17/1	17/1	1.00
Age (years)	66 ± 7	69 ± 9	0.34
Weight (kg)	84 ± 12	85 ± 14	0.88
BMI (kg/m^2)	26.3 ± 3.1	27.3 ± 4.0	0.43
Ischaemic heart disease (N (%))	13 (72)	14 (78)	0.38
Atrial fibrillation (N (%))	1 (6)	1 (6)	1.00
Clinical/laboratory			
Heart rate (beats/min)	66 ± 9	66 ± 9	0.96
Systolic BP (mmHg)	131 ± 19	131 ± 15	0.96
Diastolic BP (mmHg)	82 ± 10	79 ± 9	0.33
Fasting glucose (mmol/L)	5.8 ± 0.7	5.7 ± 0.8	0.62
2-hour OGTT glucose (mmol/L)	9.2 ± 2.6	8.9 ± 2.3	0.72
HbA_{1c} (%)	5.8 ± 0.3	5.8 ± 0.4	0.62
HOMA-IR	1.76 [1.22; 3.12]	1.68 [0.77; 2.40]	0.67
Insulin levels (pmol/L)	49 [34.5; 88.5]	43 [23.5; 67]	0.54
eGFR mL/minutes/1.73 m^2	89 ± 18	82 ± 22	0.29
NYHA-class 1/2/3/4 N	10/8/0/0	12/5/1/0	0.49
Pet parameters			
MBF rest (mL/g/minutes)	0.75 ± 0.17	0.80 ± 0.18	0.36
MFR	2.74 ± 1.10	2.47 ± 1.13	0.48
MGU global (μmoL/g/minutes)	0.26 ± 0.08	0.26 ± 0.10	0.92
Echocardiografic parameters			
LV ejection fraction (%)	33.1 ± 7.1	34.9 ± 9.2	0.54
Global longitudinal strain (%)	−11.8 ± 2.7	−11.3 ± 3.6	0.63
E/A ratio	1.22 ± 0.72	1.48 ± 1.07	0.39
E/e' (lateral) ratio	10.0 ± 5.2	12.9 ± 8.1	0.22
Treatment			
ACE-I/ARB (N (%))	17 (94)	17 (94)	1.00
Platelet inhibitors (N (%))	13 (72)	17 (94)	0.18
Beta-blockers (N (%))	18 (100)	15 (83)	0.23
Diuretics (N (%))	10 (56)	15 (83)	0.15
Loop diuretic dosage (mg/day)	71 ± 60	48 ± 30	0.31
MRA (N (%))	10 (56)	9 (50)	1.00
Statin (N (%))	15 (83)	18 (100)	0.84
ICD/CRT/CRT-D (N)	6/0/7	7/1/6	1.00

Data are mean ± standard deviation (SD) or median [25%; 75%]. *BMI*, body mass index; *BP* blood pressure; *OGTT* oral glucose tolerance test; *eGFR*, estimated glomerular filtration rate; *MBF*, myocardial blood flow; *MFR*, myocardial flow reserve; *MGU*, myocardial glucose uptake; *LV*, left ventricle; *ACE-I*, angiotensin converting enzyme inhibitors; *ARB*, angiotensin-2 receptor blockers; *MRA*, mineralocorticoid receptor antagonists; *ICD*, implantable cardioverter-defibrillator; *CRT*, cardiac resynchronization therapy; *CRT-D*, implantable cardioverter defibrillators with pacing capabilities

groups ($P = 0.98$) (Table 3). We observed no interaction of IGT on changes in either MGU ($P = 0.88$), MBF ($P = 0.92$) at rest, or MFR ($P = 0.30$). Furthermore, there was no effect on either Ki ($P = 0.20$) or SUV ($P = 0.11$) by liraglutide treatment as compared to placebo, or interaction of cause of heart failure (non-ischemic vs ischemic) on changes in MGU ($P = 0.86$) or MFR ($P = 0.37$).

The raw uptake (SUV) at baseline and follow-up from a participant treated with liraglutide is shown in Figure 4A, B, and the fitting and time-activity curves is shown in Figure 4C. MGU correlated with both Ki ($r^2 = 0.86$) and SUV ($r^2 = 0.63$).

No association was found between changes in MGU and baseline in HbA1c ($P = 0.20$), fasting glucose levels ($P = 0.35$), HOMA-IR ($P = 0.29$), or 2-hour

Table 2. Changes in clinical, laboratory and echocardiographic characteristics from baseline to end of study in participants completing the study

Change in clinical, echocardiographic and laboratory data							
	Liraglutide (N = 16)			Placebo (N = 16)			
	Baseline	Follow-up	Change (*P* value)	Baseline	Follow-up	Change (*P* value)	Liraglutide vs placebo (*P* value)
Weight (kg)	84.9 ± 3.2	83.3 ± 2.9	−1.5 ± 0.7 (0.03)	86.5 ± 3.6	86.8 ± 3.8	0.3 ± 0.4 (0.54)	−1.8 ± 0.8 **(0.03)**
Heart rate (beats/minutes)	66.1 ± 2.4	72.1 ± 2.8	6.1 ± 1.7 (0.003)	64.8 ± 2.3	63.5 ± 1.7	−1.3 ± 1.6 (0.46)	7.4 ± 2.4 **(0.004)**
Systolic BP (mmHg)	130.1 ± 4.8	122 ± 3.5	−7.6 ± 4.1 (0.08)	130.5 ± 3.7	131.3 ± 3.7	0.8 ± 3.5 (0.82)	−8.4 ± 5.4 (0.13)
Diastolic BP (mmHg)	81.0 ± 2.6	75.1 ± 2.3	−5.9 ± 2.2 (0.02)	79.8 ± 2.1	78.3 ± 2.3	−1.5 ± 1.9 (0.43)	−4.4 ± 2.9 (0.14)
LV ejection fraction (%)	33 ± 2	32 ± 2	−1 ± 2 (0.69)	35 ± 3	38 ± 2	3 ± 1 (0.001)	−4 ± 2 (0.09)
Global longitudinal strain (%)	12.0 ± 0.7	10.2 ± 0.6	−1.8 ± 0.6 (0.01)	11.9 ± 0.8	11.1 ± 0.7	−0.8 ± 0.4 (0.05)	1.0 ± 0.7 (0.19)
Fasting p-glucose (mmol/L)	5.9 ± 0.2	5.6 ± 0.1	−0.3 ± 0.2 (0.13)	5.8 ± 0.2	5.9 ± 0.2	0.1 ± 0.1 (0.37)	−0.4 ± 0.2 (0.08)
2-hour p-glucose (mmol/L)	9.6 ± 0.6	7.1 ± 0.5	−2.5 ± 0.5 (<0.001)	8.8 ± 0.6	8.4 ± 0.6	−0.4 ± 0.5 (0.42)	−2.1 ± 0.7 **(0.004)**
HbA_{1c} (%)	5.8 ± 0.1	5.6 ± 0.1	−0.2 ± 0.1 (0.03)	5.8 ± 0.1	5.8 ± 0.1	0.1 ± 0.1 (0.45)	−0.3 ± 0.1 **(0.03)**
HOMA-IR	1.76 [1.22; 3.79]	1.85 [1.27; 3.53]	−0.2 ± 0.5 (0.69)	1.71 [1.23; 2.60]	2.00 [1.20; 2.89]	0.2 ± 0.3 (0.59)	−0.4 ± 0.6 (0.52)

Bold highlights measures that differ significantly ($p < 0.05$) in terms of changes from baseline to follow-up between the groups
Data are mean ± standard error (SER) or median [interquartile range]. *BP*, blood pressure; *LV*, left ventricle

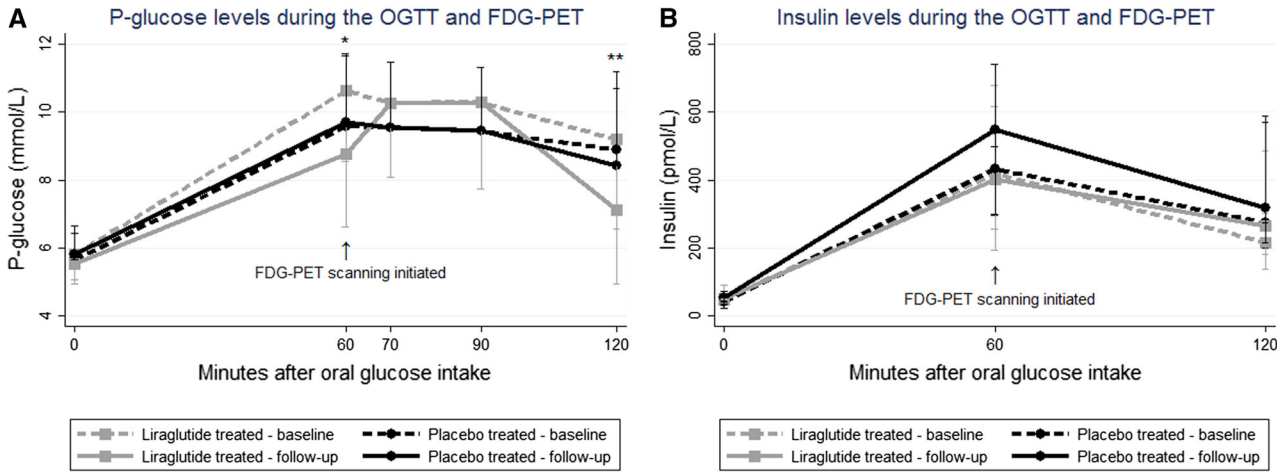

Figure 2. Glucose (**A**) and insulin (**B**) levels measured at $T = 0$, $T = 60$, and $T = 120$ minutes during the OGTT. **A** The glucose levels (mean ± SD) did not differ between groups at baseline ($P = 0.30$), whereas there was a significant decrease in the liraglutide treated group as compared to the placebo treated group from baseline to follow-up ($P = 0.005$). This difference was present both at $T = 60$ minutes ($P = 0.001$(*)) and at $T = 120$ minutes ($P = 0.002$(**)). **B** The insulin levels (median [25%; 75%]) did not differ between groups at baseline ($P = 0.18$), and there was no difference with regard to changes from baseline to follow-up between the groups ($P = 0.93$). (*OGTT*, oral glucose tolerance test).

peak glucose levels ($P = 0.45$) in the liraglutide treated group.

Outcome Measures: Regional Data

We observed a minor increase with regard to changes in MBF at rest (0.08 ± 0.03 ml/g/minutes) in segments with preserved contractility between the groups. This difference was due to a decrease in the placebo group (−0.05 ± 0.02 ml/g/minutes). However, changes in regional MGU and MFR did not differ between the groups, irrespective of contractility and viability (Table 3).

DISCUSSION

The present double-blind, randomized study investigated the effect of liraglutide on MGU during oral glucose intake, MBF and MFR in patients with HF. After 24 weeks of treatment, we observed no difference in global MGU or MBF between the two groups.

Liraglutide and MGU

In chronic HF patients, low MGU may reduce myocardial efficiency[25] and is associated with a poor prognosis.[14] Increasing MGU may therefore be beneficial. In animal studies of heart failure, GLP-1 increases MGU[9,26,27] due to enhanced GLUT expression on cardiomyocytes by akt-independent pathways that are distinct from those of insulin action.[2,4,9] Such changes are known to shift the myocardium towards a more energetically efficient substrate metabolism.[28] This shift demonstrates the direct metabolically beneficial effect of GLP-1 in these experimental models. Even so, human studies have shown conflicting results on the effect of GLP-1 on MGU.[5,7,9] However, placebo-controlled studies show that GLP-1 increases global MGU in both healthy test subjects[5] and patients with T2D,[6] but not in HF patients during HEC.[7] The former studies in healthy test subjects and T2D patients demonstrate that the effect of GLP-1 on global MGU is influenced by the degree of insulin resistance.[5,6] Hence, GLP-1 increases global MGU more in patients with whole-body insulin resistance than in those with normal insulin sensitivity. These findings are intriguing because insulin resistance is frequent in patients with HF despite no overt T2D,[29] and insulin resistance is associated with decreased MGU.[21] The lack of increase in MGU in the previous mentioned albiglutide study performed in HF patients could be due to the fact that no patients had T2D or that the applied HEC masked any potential effect that albiglutide may have caused. This is supported by an animal study that demonstrated an 8-fold increase in MGU by insulin as compared to an increase in MGU of less than twofold by GLP-1 analogs.[28] However, until now it is still undetermined to what extent global and regional MGU is affected by GLP-1 during daily living. Thus, in the present study, we simulated a daily-life situation using oral glucose intake to examine MGU. We

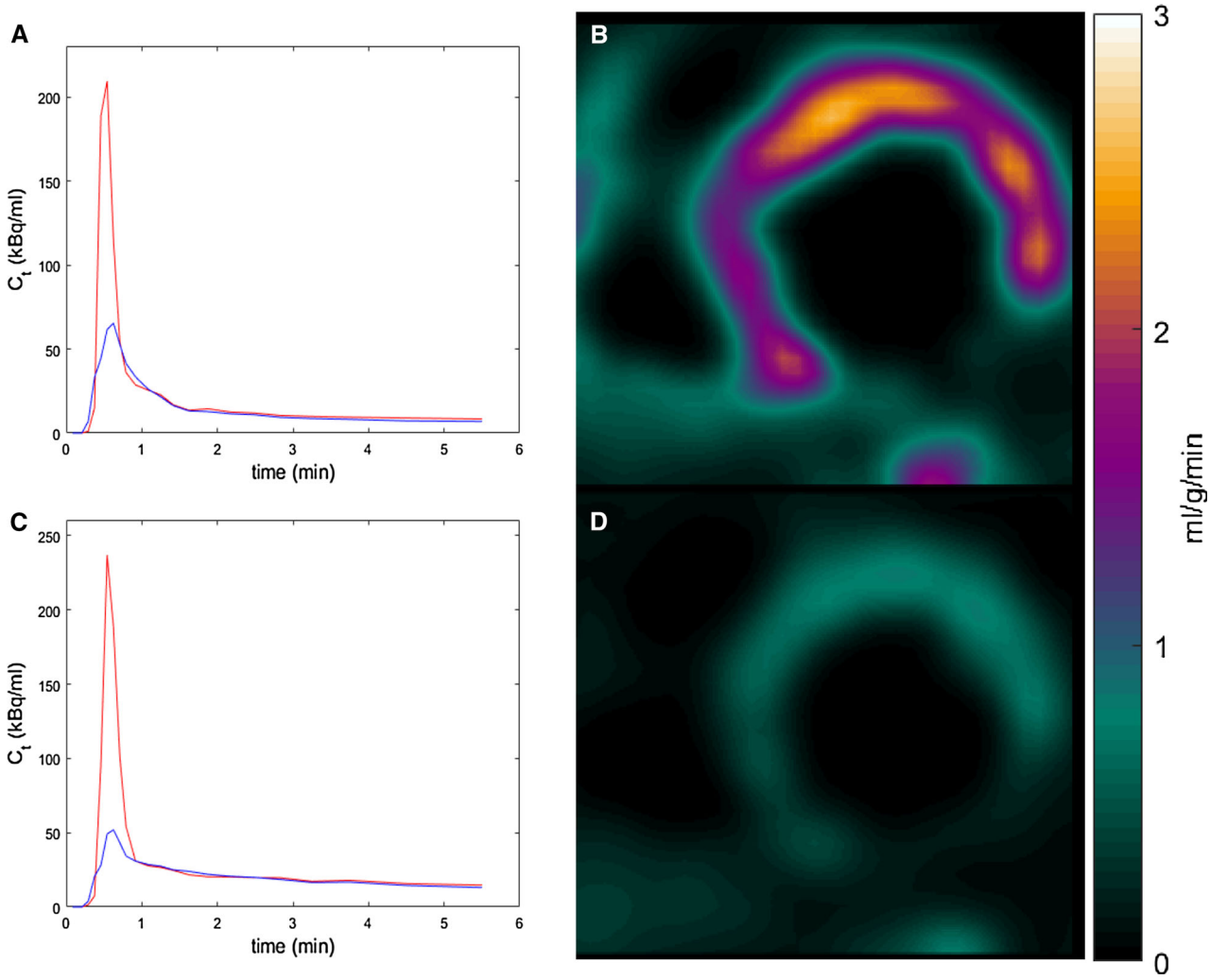

Figure 3. Time-activity curves and parametric images of H20-PET. Time-activity curves and short-axis parametric images during adenosine stimulated hyperemia (**A**+**B**) and at rest (**C**+**D**). The *red lines* represent arterial blood activity and the *blue lines* represent tissue activity. Parametric images are shown with a color map ranging from 0 mL/g/minutes (*black*) to 3 mL/g/minutes (*white*). (C_1(kBq/mL): kilobecqueral per mL.).

found that the global MGU was marginally higher than in previous studies performed in healthy controls and patients with T2D (0.15-0.20 μmol/g/minutes)[5,6] but similar to that in previous HF studies (0.21-0.26 μmol/g/minutes)[30] which may demonstrate the myocardial metabolic shift HF patients experience during the course of HF. Despite a decrease in the 2-hour peak glucose levels, we found no overall effect of liraglutide treatment on MGU. However, this decrease in glucose levels during the OGTT may merely reflect delayed gastric emptying[31] as HOMA-IR was not affected by liraglutide treatment. It could be speculated that chronic HF patients with insulin resistance may increase MGU during liraglutide treatment, but we observed no interaction of IGT on the results or any association between baseline HOMA-IR, HbA1c, or 2-hour peak glucose levels and changes in MGU.

Hence, the present findings do not support any glucometabolic effect on the failing myocardium by liraglutide treatment, but demonstrates its glucose-lowering properties in chronic HF patients even in the absence of T2D.

Liraglutide and Myocardial Blood Flow

In the present study, we chose to evaluate MFR for several reasons. Firstly, low MFR is a well-known prognostic marker for a poor prognosis in HF patients as

Table 3. Changes in PET findings from baseline to end of study in participants completing the study

	Positron emission tomographic data						
	Liraglutide			Placebo			
	Baseline	Follow-up	Change (*P* value)	Baseline	Follow-up	Change (*P* value)	Liraglutide vs placebo (*P* value)
MGU (μmol/g/min)							
Global (N = 32)	0.26 ± 0.02	0.26 ± 0.02	0.00 ± 0.03 (0.97)	0.26 ± 0.02	0.26 ± 0.02	0.00 ± 0.03 (1.00)	0.00 ± 0.04 (0.98)
Segments-PC (N = 204)	0.27 ± 0.01	0.27 ± 0.01	0.00 ± 0.01 (0.90)	0.30 ± 0.01	0.28 ± 0.01	0.02 ± 0.01 (0.05)	−0.02 ± 0.01 (0.18)
Segments-DV (N = 218)	0.29 ± 0.01	0.27 ± 0.01	−0.02 ± 0.01 (0.09)	0.31 ± 0.01	0.27 ± 0.01	−0.03 ± 0.01 (0.003)	0.01 ± 0.01 (0.42)
Segments-DNV (N = 90)	0.17 ± 0.01	0.12 ± 0.01	−0.05 ± 0.01 (<0.001)	0.16 ± 0.01	0.11 ± 0.01	−0.05 ± 0.02 (0.003)	0.00 ± 0.02 (0.81)
Global Ki (N = 32)	0.026 ± 0.003	0.034 ± 0.003	0.008 ± 0.003 (0.04)	0.030 ± 0.003	0.037 ± 0.003	0.002 ± 0.003 (0.64)	0.006 ± 0.005 (0.20)
Global SUV (N = 32)	5.90 ± 0.55	6.75 ± 0.45	0.84 ± 0.45 (0.08)	6.81 ± 0.61	6.52 ± 0.54	−0.29 ± 0.52 (0.59)	1.13 ± 0.69 (0.11)
MBF (mL/g/minutes)							
Global (N = 31)	0.74 ± 0.04	0.75 ± 0.06	0.01 ± 0.05 (0.83)	0.80 ± 0.05	0.78 ± 0.05	−0.02 ± 0.05 (0.75)	0.02 ± 0.07 (0.76)
Segments-PC (N = 198)	0.75 ± 0.02	0.78 ± 0.03	0.04 ± 0.02 (0.23)	0.80 ± 0.02	0.76 ± 0.02	−0.05 ± 0.02 (0.03)	0.08 ± 0.03 **(0.02)**
Segments-DV (N = 208)	0.79 ± 0.02	0.79 ± 0.03	0.00 ± 0.03 (0.90)	0.82 ± 0.02	0.85 ± 0.02	0.03 ± 0.03 (0.22)	−0.03 ± 0.04 (0.33)
Segments-DNV (N = 90)	0.57 ± 0.03	0.60 ± 0.05	0.03 ± 0.04 (0.38)	0.68 ± 0.03	0.66 ± 0.03	−0.02 ± 0.04 (0.59)	0.00 ± 0.03 (0.33)
MFR							
Global (N = 30)	2.78 ± 0.30	3.04 ± 0.26	0.26 ± 0.22 (0.25)	2.45 ± 0.30	2.66 ± 0.25	0.21 ± 0.24 (0.40)	0.05 ± 0.32 (0.89)
Segments-PC (N = 190)	2.75 ± 0.14	3.02 ± 0.16	0.27 ± 0.14 (0.05)	2.47 ± 0.13	2.65 ± 0.11	0.18 ± 0.10 (0.09)	0.09 ± 0.17 (0.59)
Segments-DV (N = 208)	3.23 ± 0.14	3.16 ± 0.16	0.25 ± 0.18 (0.17)	2.70 ± 0.12	2.82 ± 0.12	0.12 ± 0.12 (0.27)	0.11 ± 0.09 (0.25)
Segments-DNV (N = 82)	2.01 ± 0.21	2.49 ± 0.19	0.49 ± 0.21 (0.03)	2.14 ± 0.18	2.45 ± 0.18	0.31 ± 0.16 (0.06)	0.18 ± 0.27 (0.52)

Bold highlights measures that differ significantly ($p < 0.05$) in terms of changes from baseline to follow-up between the groups
Data are mean ± standard error of mean. *MBF*, myocardial blood flow; *MFR*, myocardial flow reserve; *MGU*, myocardial glucose uptake; *Ki*, influx rate constant of 18F-FDG; *SUV*, standard uptake value; *PC*, preserved contractility; *DV*, dysfunctional viable; *DNV*, dysfunctional nonviable

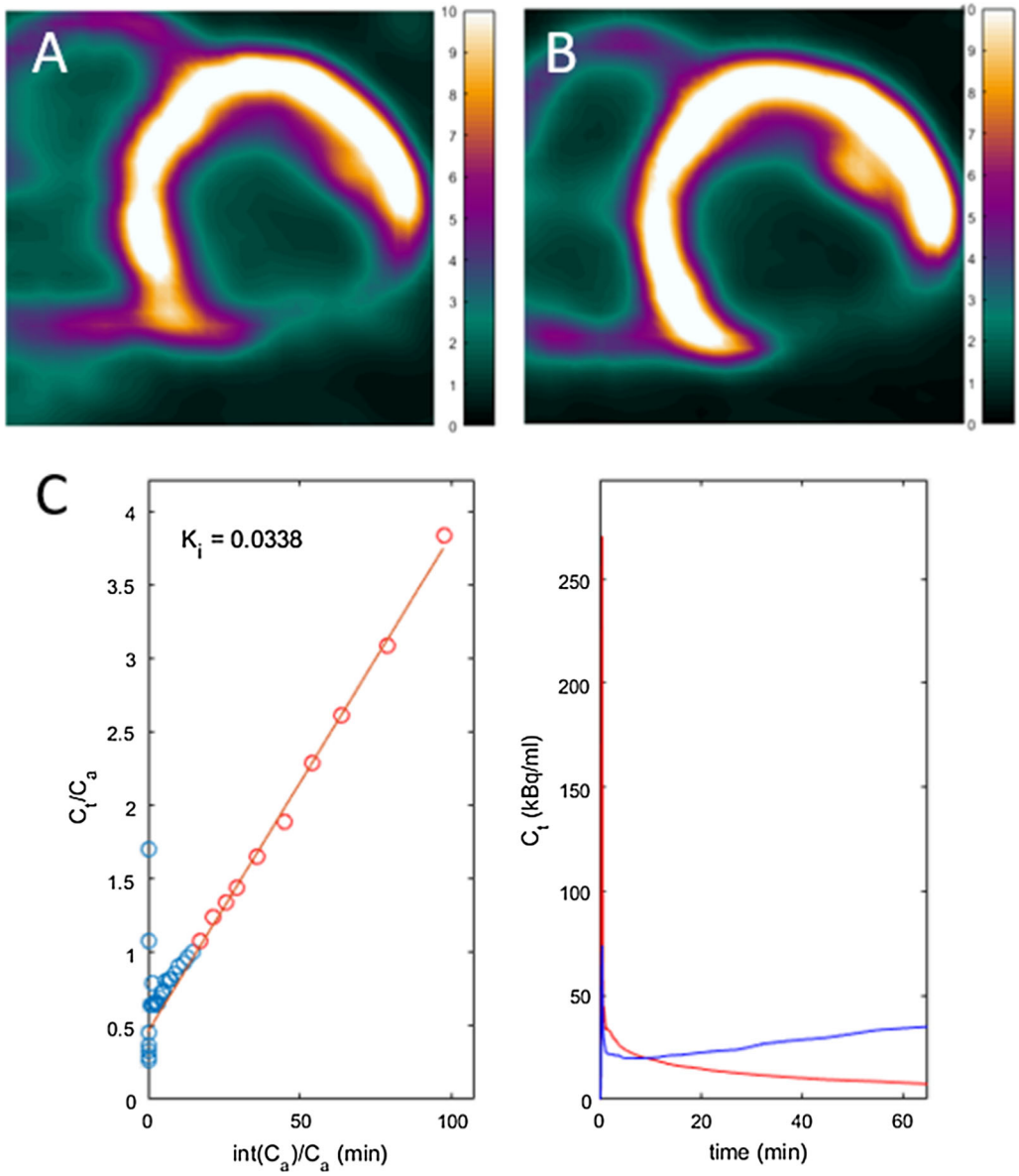

Figure 4. SUV, fitting and time-activity curves of 18F-FDG uptake. Short-axis raw myocardial uptake (SUV) of 18F-FDG at baseline (**A**) and follow-up (**B**) of a participant treated with liraglutide. The *scale bars* refer to SUV. The fitting (**C** *left*) and time-activity curves (**C** *right*) at baseline are shown. **C** *left* The *blue circles* represent datapoints from $T = 0$ to $T = 10$ minutes whereas the *red circles* represent datapoints from $T = 10$ to $T = 60$ minutes. The best fit (Ki) is 0.0338 (*red lines*) and based on data from $T = 10$ to $T = 60$ minutes after injection. Ct/Ca is the ratio between tissue (Ct) and blood activity (Ca). int(Ca)/Ca is the ratio between the integrated activity of the blood (int(Ca)) and the blood activity (Ca) at each time point. **C** *right* the *red line* represents blood activity and the *blue line* represents tissue activity. (C_1(kBq/mL): kilobecqueral per mL).

it indicates microvascular dysfunction and obstructive coronary artery disease.[15] Secondly, it has been demonstrated that GLP-1 increases myocardial perfusion in the isolated heart model,[32] and thirdly, due to its protection of the microvasculature from oxidative stress and apoptosis[33] and preservation of MFR after cardiac arrest.[3] Despite these intriguing animal results, GLP-1 infusion had no short-term effect on MBF[26] in a tachycardia-induced, dilated cardiomyopathy model. However, a small clinical short-term study (N = 8)

where quantitative PET methods were used showed that GLP-1 administration improved resting MBF by 24% in patients with T2D and no coronary heart disease or HF,[6] but MFR was not evaluated. Similar results were found in healthy subjects in a study where semi-quantitative contrast-enhanced echocardiography was used.[8] However, these findings could not be reproduced either in a short-term[9] or in a long-term study that evaluated MFR after 10 weeks of treatment with liraglutide in patients with T2D.[10] In a recently published study, the authors were not able to demonstrate any effect of 12 weeks of treatment with an GLP-1 analog on myocardial oxygen consumption[7] in HF patients. However, functional capabilities of the vasculature in terms of MFR or MBF were not reported. In the present study we now extend these previous findings, and we demonstrate that there are no effect of liraglutide treatment on either global or regional MFR after 24 weeks of treatment despite an increase in heart rate. A minor preservative effect of liraglutide on MBF at rest in normal contracting segments cannot be excluded($P = 0.02$, Table 3). However, this effect was driven by a minor decrease of approximately 5% in myocardial segments of the placebo group ($P = 0.03$, Table 3). Hence, this secondary finding may likely be a type 1 error due to multiple comparisons, and therefore, should be interpreted with caution.

The LEADER trial was a large multicentre trial evaluating the effect of liraglutide treatment in patients with T2D diabetes.[13] Liraglutide treatment was associated with a decrease in the rate of all-cause death. LEADER did not reduce the rates of AMI, stroke or hospitalization for heart failure. Approximately 16% of the enrolled patients had symptomatic CHF (NYHA-class 2-3), but importantly, no data on LVEF were reported. Hence, in the LEADER trial, it is unknown whether the patients had CHF with reduced or preserved LVEF. In the LIVE[11] and FIGHT[12] studies, only patients with HF and reduced LVEF were enrolled and the minority had T2D. LVEF did not improve during liraglutide treatment, and there was an increase in adverse events which was due mainly to an increase in arrhythmias. The present study shows that the events seen in the LIVE study are unlikely to be caused by decreases in myocardial perfusion and MGU or an increase in scar burden as determined by PTI. On the other hand, the failure of liraglutide to improve MGU and MBF might explain the failure to improve LVEF in the LIVE study.

Study Limitations

We observed no association between the level of insulin resistance in terms of HOMA-IR and changes in MGU. This may be due to the exclusion of patients with more deranged glucose metabolism, i.e., T2D. For the same reason, it remains to be studied whether the effects of liraglutide on MGU, MBF, and MFR are different in HF patients with T2D as metformin treatment is often prescribed to T2D patients and may have synergistic protective effects with liraglutide on endothelial function.[34] However, we find it unlikely that such patients would behave differently with regard to perfusion as the present findings in HF patients are in accordance with those of a previous study in which T2D patients on metformin treatment were treated for 10 weeks with liraglutide.[10]

In the present study, we chose to apply OGTT during the ^{18}F-FDG-PET scanning to simulate a daily-life condition. Previous studies predominantly applied insulin infusion during ^{18}F-FDG-PET scanning.[5-7,9] The present method may have methodological disadvantages as the glucose and insulin levels are not fixed during the examination. However, we find it important to evaluate MGU during a simulated daily-life condition like an OGTT and not to overwhelm any potential effect of GLP-1 on MGU using HEC. However, it remains unknown whether the use of an OGTT during the 18F-FDG-PET or the fact that the patients' HbA1c levels were within the normal range could explain the discrepancies between our findings and those of others, but the present results regarding MGU are consistent with those from others using HEC in HF patients.[7]

No data were available for power calculation regarding quantitative 18F-FDG uptake in the present study population. However, the size of the present study is in a similar range of that of previous investigation regarding MGU in patients with heart disease (N = 21, [7] N = 53[30]).

In the present study, the average MFR was 2.5 and 2.7 in each group, respectively. It is unknown to what extend liraglutide may affect MFR and MBF in participants with lower MFR. However, this would require a different design in which low MFR would be an inclusion criteria. In addition, the possibility of a type 2 error regarding MBF and MFR cannot be excluded, but the size of the present study is similar to that of previous clinical, randomized studies showing an effect of beta-blockers on MBF in HF patients.[35]

CONCLUSION

Despite a reduction in HbA1c and lowering of glucose levels during an OGTT, liraglutide did not affect global or segmental MGU or MFR in HF patients without T2D. These findings may explain the absence of beneficial effects in the LIVE and FIGHT[12] studies, but they also demonstrate that the increase in cardiac events in these studies does not involve decreases in MGU or MFR.

NEW KNOWLEDGE GAINED

The present double-blinded randomized clinical study is the first to evaluate the effect of liraglutide treatment on myocardial perfusion and glucose uptake in heart failure patients. The findings are novel, and demonstrate that the increase in adverse events observed in the LIVE and FIGHT studies during liraglutide treatment in chronic heart failure patients were not ascribed to changes in myocardial perfusion or glucose uptake.

Disclosures

Anders Jorsal and Lise Tarnow hold shares in Novo Nordisk A/S. Caroline Kistorp has been a principal or sub-investigator for the following companies: MSD, Novo Nordisk, Novartis, GSK and Astra Zeneca, and has participated in advisory boards for MSD and Astra Zeneca and Novo Nordisk. Henrik Wiggers has been a principal or sub-investigator in studies involving the following pharmaceutical companies: MSD, Bayer, Daiichi-Sankyo, Novartis, Novo Nordisk, Sanofi-Aventis and Pfizer. Ida Gustafsson has been principal or sub-investigator in studies involving the following pharmaceutical companies: Novartis, Janssen, GSK, MSD and Astra-Zeneca and has participated in an advisory board meeting at Boehringer-Ingelheim and Novo Nordisk. Lise Tarnow has conducted studies with, served as a consultant for and is a member of advisory boards for Novo Nordisk. The authors declare no other conflicts of interests.

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