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Results: Twenty four patients (15 women), aged 52 (11.7) years, with 8.7 (5.8) years' diabetes duration, BMI 34.98 (6.2) Kg/m2 and HbA1c 8.2 (0.68)% were randomised to liraglutide (12) or placebo. There were no differences in VO2máx (17.98 (4.8) vs 15.90 (4.96) ml/Kg/min, p>0.1), in the VE/VCO2 slope (30.18 (4.8) vs 32 (4.49)), left ventricular ejection fraction, or in the 6 min walk test (530.7 (86) vs 503.9 (84) metres) at 6 months. HbA1c was lower (6.7 vs 7.7% p=0.005) and there was a trend towards lower maximal systolic blood pressure during the ergometry (171.7 (24.4) vs 192.5 (25.6), p=0.052) in the liraglutide group at the end of the study. There were no severe adverse events.
Conclusions: In this trial, liraglutide improved glycaemic control in type 2 diabetes, but did not have significant effects on physical performance or myocardial function.

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Effect of Liraglutide on Physical Performance in Type 2 Diabetes (LIPER2): Results of a Randomized, Double-blind, Controlled Trial.

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Abstract:

Aims: To assess the effect of the GLP1-analogue liraglutide on measures of cardiac function and physical performance in patients with type 2 diabetes.

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Conclusions: In this trial, liraglutide improved glycaemic control in type 2 diabetes, but did not have significant effects on physical performance or myocardial function.

Keywords: Randomized controlled trial. Ergometry. Maximal oxygen consumption. Ventricular function. Diabetes. GLP1-agonist.

Abbreviations: GLP1: Glucagon-like peptide 1. LIPER2: Effect of LIraglutide on physical PERformance in type 2 diabetes. ITT: Intention-to-treat. PP: Per-protocol. VO2max: Maximal Oxygen consumption. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. RER: Respiratory exchange ratio.

VE/VO2máx: ventilatory equivalent for oxygen (at the time of maximal oxygen consumption). VE/VCO2AT: ventilatory equivalent for carbon dioxide (at the time of anaerobic threshold).

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1. Introduction

Glucagon-like peptide 1 (GLP1) analogues are approved for the treatment of type 2 diabetes and obesity, based on their glucose and weight-lowering effects. Known cardiovascular effects include reduced blood pressure [1-3] and increased pulse rate. [2-4] Recently, large clinical trials have been performed to assess their effect on cardiovascular events. [5-7] Globally, GLP1-analogues seem to be neutral or protective on the cardiovascular system in patients with type 2 diabetes.

Fewer studies are available specifically assessing their effect on physical performance and measures of myocardial function. At the time of the design of this study, trials in humans were scarce and their results controversial. Two small, randomised, controlled trials showed positive effects of acute GLP1 infusion in patients with ischaemic heart disease, [8, 9] but a larger trial did not show an effect on left ventricular ejection fraction or infarct size with the intravenous administration of the GLP1 analogue exenatide. [10] To our knowledge, no trial has previously assessed the effect of a GLP1 analogue on physical performance.

The aim of this trial was to assess the effect of liraglutide, a GLP1 agonist, on clinically relevant measures of physical performance and myocardial function in patients with type 2 diabetes.

2. Subjects and Methods

A. Trial design and oversight

LIPER2 is a single-center, randomised, double-blind, placebo-controlled, parallel group, phase IV trial, assessing the effect of liraglutide on physical performance and myocardial function. LIPER2's design has been published [11] and registered (https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-005197-63). Participants with type 2 diabetes were randomised in a 1:1 ratio, to receive 1.8 mg liraglutide (Victoza (R), Novo Nordisk) or placebo daily for 6 months.

The study was approved by the Ethics Committee of the Complejo Hospitalario Universitario Insular Materno Infantil and by the Spanish Medical Agency. Before inclusion, patients received oral and written information and a written, informed consent document was signed by each participant. Data accuracy and compliance with the protocol, with Good Clinical Practice International Guidelines and with national regulations was assessed by external, qualified staff from CRAnarias SL, Las Palmas de Gran Canaria, Spain.

The LIPER2 trial was approved and funded by Novo Nordisk, Bagsvaerd, Denmark. The investigators designed and conducted the study, performed all study analyses and have written and are responsible for the contents of this manuscript.

The manufacturer had no role in the collection, analysis, interpretation, writing, or publication of the data. The principal investigator has full access to all the data and the final responsibility for the decision to submit for publication.

B. Patients

Patients were identified and invited to participate in the outpatient clinics at the Endocrinology Department and at the primary care centres to which the hospital is the referral centre. Inclusion and exclusion criteria have been described before [11]. Briefly, we included patients with type 2 diabetes, treated with oral agents (including metformin if tolerated and not contraindicated), a maximum of 2 intermediate or long acting insulin injections per day or a combination of both and an HbA1c between 7% and 10%. The main exclusion criteria were severe renal, cardiac or hepatic failure, existing or planned pregnancy or breastfeeding or inadequate contraception and intolerance, allergy or contraindication to the treatment with liraglutide (e.g: history of pancreatitis). Participants were also excluded if they were treated with GLP1 agonists or dipeptidyl-peptidase 4 (DPP4) inhibitors in the 3 months before screening (to avoid potential overlap in the mechanism of action), if they had exercise-induced myocardial ischaemia, planned revascularisations or were not able to perform a cycle ergometry.

C. Procedures

Patients were assessed at a screening visit, after signing written, informed consent. If they fulfilled all of the inclusion criteria and none of the exclusion criteria, a baseline visit was be performed within one month of the screening visit and participants were randomized. Patients started the assigned intervention and were then assessed again at 3 months (safety assessment) and 6 months after treatment initiation. Additional telephone contact was used to evaluate tolerance and the need for concomitant treatment adjustment within the two weeks following study treatment initiation.

In patients with an HbA1c >8% at the 3-month visit, insulin could be started or adjusted if deemed appropriate. Concomitant oral agents could be reduced in case of hypoglycemia.

D. Outcomes

Primary end-point

The primary end-point was fitness, or physical performance, defined as the maximal oxygen consumption (VO2max; Breeze Suite 6.4, Medgraphics, Medical Graphics Corporation, Saint Paul, MN, USA) during a

cycle ergometer test (Ergoselect, Ergoline, Bitz, Germany) performed at the end of the study. An incremental protocol was used, where the first 3 minutes were performed without resistance and the latter was then increased by 10-20 watt/minute (adjusted according to weight, height, age and ethnicity). The total duration of the test rarely exceeded 10-12 minutes. Before the test was started, the procedure was described in detail and participants signed written informed consent. Ergometry and VO2 máx measurement were performed according to international guidelines, at the Rehabilitation and Physical Medicine Department, at baseline and at the end of the study, as previously described. [11] Maximal exertion ergometry (HR > 85% theorical maximum and RER > 1.10) was attempted and participants were encouraged to perform as well as they could.

Secondary end-points

Secondary endpoints included additional, fitness-related variables, recorded during the ergometry, a 6-minute walk test and transthoracic echocardiograpy. [11] VE/VCO2 slope, a marker of ventilatory efficiency, was added to the initial list of secondary end-points, following recent guidelines. [12] This was possible for 10 participants at baseline and 11 at follow-up. Glycaemic control was assessed using HbA1c, measured by HPLC, using a NGSP/DCCT-based standard, and examining the patients' glucose registers, as well as questioning them about hypoglycaemic episodes, daily insulin dose and other concomitant medication. All laboratory measurements were performed in the hospital's Biochemistry Department. Quality of life was assessed (*Spain (Spanish) v.2 © 2009. EQ-5D-5L, EuroQoL Foundation, Rotterdam, The Netherlands)* and spontaneous physical activity was recorded using a physical activity Holter (SenseWear Pro, BodyMedia, Pittsburgh, PA, USA) for three days. The most complete (usually the second) day was assessed.

The primary and secondary endpoints were assessed at baseline and at the end of the study (6 months), except for those related to glucose control, which were evaluated at the 3 months visit, too.

Safety end-points

The safety end-points included standardized adverse event (AE) reporting, blood count, liver and kidney function, electrolytes, lipase, amylase, CA19.9 and calcitonin. A general physical examination was

performed at baseline and at the end of the study. A pregnancy test was performed on all women with childbearing potential before randomisation and during follow-up. In addition, at the end of the study, an endoscopic ultrasound was offered to the patients, in order to assess pancreatic architecture. A separate, standard consent form was provided and signed before the examination.

E. Analysis

After completion of the study and final external monitoring, the treatment assignment list was opened by a person, external to the study, and the two treatment groups were separated for blind analysis by study investigators. Analyses were performed on an intention-to-treat (ITT) and per-protocol (PP) basis, as described earlier in the statistical plan [11] For the ITT analysis, all randomised subjects were included, regardless of whether they finished the study or not and whether they took the medication throughout the study or not; when a variable was missing at follow-up, the last available observation was carried forward. For the PP analysis, only the results of the patients who took their treatment and completed the study were analysed. No adjustment was made for missing variables in this case.

Comparison between the intervention and placebo groups were performed using chi-squared (qualitative data), Student's T test (quantitative, Gaussian distribution) and Mann-Whitney's U (quantitative, non-Gaussian). Paired analysis was also performed to compare beginning and end of treatment in each group (Student's t and Wilcoxon's test). A bilateral $p<0.05$ was considered significant.

Sample size

Sample size calculation has been described in the statistical protocol [11]. Briefly, we estimated that including 15 patients per group would allow us to detect a difference between groups of 5ml/Kg*min in VO2max with 98% power and bilateral alfa of 5%. This is in the lower range of the effect that has been reported in older men participating in training programmes. [13] Even if an unexpectedly high drop-out rate of 25% would happen, the power to detect this difference between groups would still be of 90%.

3. Results

The trial was performed between June 2013 and August 2016. Recruitment was slower than expected, especially due to the frequent use of DPP4-inhibitors (listed as an exclusion criteria) in our population with type 2 diabetes. The study was prolonged as long as the expiry date of a second study treatment lot allowed. A total of 35 participants were screened, 24 were randomized (we initially aimed at 30) and 23 completed the study (see figure 1).

Of the 11 patients excluded after screening, 3 withdrew consent, 4 were excluded because of an HbA1c>10% at the baseline visit, 2 due to an HbA1c<7%, 1 because of a diagnosis of pancreatitis according to the review of his clinical records and 1 because she could not perform the baseline cycloergometry due to knee osteoarthritis. Of the 24 randomised patients, 1 stopped taking the study drug (placebo) a few weeks into the study because of fear of pancreatic cancer, 1 interrupted the treatment (liraglutide) 12 weeks into the study due to persistent side effects despite dose reduction and 1 was lost to follow-up after the baseline visit (placebo group) due to travel.

One patient received statin treatment at the baseline visit and her lipid profile and apolipoprotein B concentration in the 6-month visit were discarded and replaced by her baseline values. One patient had CRP values above 5, which were attributed to acute infection/inflammation and omitted for analysis. One patient (with a known diagnosis of proliferative retinopathy) could not perform the final ergometry due to active vitreal bleeding. Thus, the missing ergometry results were replaced by the baseline values in the ITT analysis.

A. Baseline features

Of the 24 randomised participants, 15 (62.5%) were women, their mean (SD) age was 52.8 (11.7) years, time since diagnosis of diabetes was 8.7 (5.8) (0-20) years, BMI 34.98 (6.2) Kg/m^2, waist girth 112.1 (11.6) cm and HbA1c 8.2 (0.68) (range 7.2-9.6)%. All were treated with metformin: 6 with sulphonylureas, 5 with insulin, 3 with both and 2 with insulin and repaglinide. No differences were found between treatment groups in sex distribution, age or diabetes duration. These and other baseline features are displayed in table 1.

B. Primary end-point

No significant differences were found between treatment groups in maximal oxygen consumption at the end of the study (see table 2)

C. Secondary end-points

Other ergometry-related variables

Of the secondary endpoints obtained from the cycloergometry, there were no stastistically significant differences at baseline or at the end of the study (see table 2). Maximal systolic blood pressure tended to be lower after treatment with liraglutide.

The increment in VO2máx was calculated by substracting the initial value from that obtained at the end of the study and compared between treatment groups. An increment of 0.167 (1.80) vs 1.008 (1.92) ml/Kg/min was seen in the placebo and liraglutide groups, respectively (p=0.20)

Six-minute walk test:

No significant differences were seen between groups at baseline or follow-up in any of the O2 saturation measurements (resting, final, minimum)[data not shown], heart rate (resting, 6min, average), meters walked (see table 2), blood pressure response to walk test or perceived exertion (Borg-scale)[data not shown]. The increment in meters walked was also calculated and compared between the treatment groups and no significant differences were found [22.2 (37.0) in the placebo vs 25.9 (34.1)m in the liraglutide group (p=0.80)].

Activity Holter (accelerometer)

No significant diferences were found at baseline or at the end of the study regarding estimated total calorie expenditure, number of steps, active time, sleep duration or METs/24h (data not shown).

Transthoracic echocardiography

Participants had an overall, normal left ventricular ejection fraction at entry [0.63 (0.06)]. A total of 33, 17 and 21% of the participants showed mild, moderate and severe ventricular hypertrophy, respectively. Regarding diastolic function, 62.5% showed grade 1 and 16.6% grade 2 dysfunction, whereas 20.8% displayed normal diastolic function. [14] No significant differences were found between treatment groups in left ventricular ejection fraction, ventricular mass or measures of diastolic function at baseline or at the end of the treatment period (see table 3). Paired analysis showed no differences between baseline and 6-month values for any of the variables in any of the treatment groups, either. Furthermore, no significant treatment effects were identified, either, assessed by the comparison of the changes in each variable, between groups (supplementary table 1).

Glycaemic control and other variables

Fasting glucose and HbA1c were significantly lower in the liraglutide group both at 3 and 6 months, although paired analysis showed that HbA1c improved significantly in both treatment groups (see table 4).

Three patients started new insulin treatment due to persistent hyperglycaemia (two in the placebo group and 1 in the liraglutide group) and in one additional patient (in the placebo group), insulin dose was increased. In 6 patients (1 in the placebo group and 5 in the liraglutide group), insulin/sulphonylurea dose was reduced during the study. No significant differences were found between groups in the average insulin dose at baseline or at the end of the study.

Anthropometric and other lab results are shown in table 5. There were some differences between treatment groups in HDL and LDL cholesterol, triglyceride and C-reactive protein already at baseline. However, paired analysis showed no significant differences for triglycerides, C-reactive protein or HDL cholesterol between baseline and the end of the study for any of the treatments.

Quality of life

No significant differences were found at baseline [76.3 (17.9) vs 74.3 (14.7) points] or at the end of the study [85.3 (13.5) vs 76.7 (16.8) points] between the placebo and the liraglutide group in the global score of the Visual Analog Scale of *EQ-5D-5L, EuroQoL* or for any of the subscales (data not shown). Paired analysis did not show significant changes in any of the groups, either.

D. Per protocol analysis

The maximal total N was reduced to 21 (20 in the ergometry, due to active vitreal haemorrhage in one of the participants). Analyses were repeated and no significantly different conclusions could be drawn, except that VO2max tended to be higher (p=0.084) and VE/VCO2AT was significantly lower at the end of the study in the liraglutide treatment group (p=0.048).

E. Safety

No serious adverse events were reported or identified during the study. Side effects are recorded in supplementary table 2. All of the patients in the liraglutide group reported some form of gastrointestinal symptom, although in 50% (6 patients) they were mild and most were self-limited. In one patient in the liraglutide group, treatment was interrupted due to side effects (gastrointestinal symptoms and hypertransaminasaemia) and in another patient, the study drug dose was reduced to 1.2mg/d (diarrhoea). Nausea was the most common symptom, followed by abdominal pain, diarrhoea and vomitting. Three patients (25%) in the liraglutide group reported upper respiratory tract infections or flu and one reported headaches.

In the placebo group, 3 (25%) patients reported gastrointestinal symptoms, although no patient interrupted treatment due to side-effects. Two patients reported upper respiratory tract infection or flu and two reported headaches. A total of 7 patients in the placebo group reported some form of adverse event during the study.

At 3 months' treatment with liraglutide, lipase was higher (p=0.039) and amylase tended to be higher (p=0.063) and at the end of the study, both amylase (p=0.012) and lipase (p<0.005) were significantly higher than in the placebo group (see table 4). No episodes of acute pancreatitis were diagnosed during the study. No differences were seen at baseline or follow-up in CA19.9 or liver enzymes. There were no significant increases in calcitonin in any of the treatment groups.

Echoendoscopy was only performed on 5 patients at the end of the study (4 in the placebo group and 1 in the treatment group). Two were normal (one in each group) and the other 3 showed indeterminate (previously unknown), chronic pancreatitis.

4. Discussion

The LIPER2 is a double-blind, placebo-controlled clinical trial assessing the effect of 6 months' treatment with liraglutide, on measures of physical performance and ventricular function in patients with type 2 diabetes who had a baseline HbA1c between 7 and 10%. The main outcome, i.e VO2 max at the end of the study, did not differ significantly between the treatment groups. The increment in VO2 max during the study, did not differ between groups, either.

Several trials assessing ventricular function have been published since the beginning of LIPER2, most using echocardiography (reviewed in [15]). However, to our knowledge, this is the first study assessing the effect of a GLP1 analogue on VO2max, the gold standard to assess cardiovascular fitness. Additional strengths of this study include its nature (placebo-controlled, randomised trial), good patient retention, the fact that no simultaneous DPP4 inhibitors were used and the extent of the study procedures, combining ergometry, echocardiography, 6-minute walk test, activity Holter, health-related quality of life and many clinical and laboratory tests.

Apart from the expected improvement in glycaemic control, a non-significant, 1 ml/Kg.min increase in VO2max was found in the liraglutide group. Furthermore, the number of steps walked during the 6 minute test increased significantly only in the liraglutide group, although the increase did not differ between the groups.

Several causes could explain this non-significant difference in the primary outcome. [16] First of all, a truely neutral effect of liraglutide on physical performance is plausible. However, sample size is certainly an issue, since it was defined to detect a larger (5 ml/Kg.min), maybe somewhat optimistic, change in VO2max. Indeed, to detect a 1-ml/Kg.min difference (SD 4.8) in VO2max, with a power of 80% and bilateral alpha of 0.05, a sample size of 726 and a multi-centre trial would have been necessary. It is reasonable to assume that there could be some minor, undetected effect (type 2 error), as pointed out by other outcomes. The treatment regimen and dosing are probably adequate, since it has previously proved a reduction in cardiovascular events and mortality in the LEADER study. [5] However, the 6-month duration might not be enough to have an effect on physical performance. A randomized trial assessing diastolic ventricular function and VO2 max in young people with type 2 diabetes treated with liraglutide or sitagliptin should soon reports its outcomes and add to existing knowledge. [17]

In patients with pre-existing, chronic heart failure, liraglutide has shown no positive effects on ventricular function. [18,19] The FIGHT trial (Functional Impact of GLP-1 for Heart Failure Treatment) assessed the effect of liraglutide (vs placebo) on clinical stability in 300 patients with pre-existing chronic heart failure and recent hospital admission. [19] No significant benefits were proved on death, new admissions due to heart failure, a 6 minute walk test, left ventricular ejection fraction or markers of myocardial function. Indeed, in the 178 patients with type 2 diabetes included in the trial, there was an almost significant trend suggesting harm [HR 1.51 (1.00-2.29), p=0.05 for the combination of death, admission to hospital due to heart failure or visit to the emergency department]. The LIVE trial assessed the effects of liraglutide (vs placebo) in 241 patients (30% with diabetes) with LVEF<=45% and stable chronic heart failure. Left ventricular systolic function was not affected by treatment, but serious cardiac events were more frequent in the intervention group. [18]

As an adjunct to exercise in patients with type 2 diabetes, liraglutide seemed to blunt some of the positive effects of the former on left ventricular diastolic function, [20] in agreement with some of the findings in the LIVE study. [18] A smaller, open, randomized trial, assigning patients with heart failure and ischaemic heart disease to liraglutide, sitagliptin or glargine, showed an improvement in left ventricular ejection fraction, 6 minute walk test and other markers of ventricular function only in the liraglutide group. [21] However, no direct comparisons were made between the treatment groups.

We are aware that this trial has some limitations, the main one being small sample size. With the inclusion of DPP4-inhibitors in the regular treatment of people with type 2 diabetes, recruitment was made more difficult, given the fact that this was an exclusion criterium, and was prolonged more than initially planned. VO2 max, our primary end-point, is very dependent on age, sex and body weight. Nevertheless, we calculated VO2 max per Kg-body weight and age and sex distribution were similar in both treatment groups. Furthermore, percentage of theoretical VO2max achieved was also considered, but did not differ between groups, either. We also used the 6 minute walk test to assess physical performance, which is very useful in patients with functional class II-III, but has a lower predictive value in NYHA class I. Despite this, a significant increase in this measure was found in the liraglutide group.

5. Conclusion

This small, randomized, placebo-controlled trial did not show a significant effect of liraglutide on VO2max or other measures of physical performance or myocardial function

6. Appendix

See supplementary tables

7. Acknowledgments

We are grateful to Novo Nordisk, Bagsvaerd, Denmark, for providing the funding, as well as the study drug and placebo, for this trial.

8. Disclosure

FNM has received speaker's fees from Novo Nordisk, MJLM from Boehringer-Ingelheim and Merck Sharpe Dome and MPAR, from Novo Nordisk, Boehringer-Ingelheim and MSD.

The LIPER2 trial was approved and funded by Novo Nordisk, Bagsvaerd, Denmark. The investigators designed and conducted the study, performed all study analyses and have written and are responsible for the contents of this manuscript. The manufacturer had no role in the collection, analysis, interpretation, writing, or publication of data. The investigators have full access to all the data and the final responsibility for the decision to submit for publication.

9. Author contributions

AMW designed the study, analysed the data and wrote the manuscript. AMW, MPA, MJL and FJN recruited and followed the patients. GM, MAL, CA and NA guided the patients in their performance and interpreted the ergometries, the 6-minute walk test and the activity Holter. HM and LS performed the echocardiographies, recorded and analysed the data obtained from them and interpreted their results. AD managed the study medication and assured the double-blind nature of the trial. AC performed the echoendoscopic studies. All of the authors have access to the data, have read the manuscript critically and accepted its final version

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Tables

437 **Table 1**: Baseline features of the 24 randomized participants

	Placebo	Liraglutide
Age (years)	52.6 (13.8)	53.2 (9.7)
Sex (N of women)	8	7
Diabetes duration (years)	7.42 (4.1)	10.0 (7.2)
Retinopathy (N)	1	2
Coronary artery disease (N)	0	2
Transient ischaemic attack (N)	0	1
Diabetes treatment (N)		
Metformin	12	12
Sulphonylurea	5	5
Repaglinide	2	0
Insulin	7	3
Hypertension (N)	7	8
Dyslipidemia (N)	5	6
Current smoking (N)	2	3
Other treatments		
Aspirin	7	7
Renin-angiotensin axis inhibitor	8	10
Statin	6	7

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439 **Table 2**: Ergometry and 6-min walk test results at baseline and at the end of the study in the participants treated with placebo and liraglutide

	Baseline	**p (vs placebo)**	**End of study**	**p (vs placebo)**	**p (vs baseline)**
Ergometry					
VO2 max (ml/Kg/min)					
Placebo	15.88 (4.91)		15.90 (4.96)		0.93
Liraglutide	16.96 (4.32)	0.41	17.98 (4.8)	0.31	0.095
Percentage of theoretical VO2max					
Placebo	76.7 (11.7)		78.2 (11.3)		0.66
Liraglutide	80.9 (12.9)	0.42	83.3 (17.7)	0.43	0.51
Duration of cycloergometry (sec)					
Placebo	691 (180)		702 (178)		0.63
Liraglutide	728 (206)	0.64	739 (214)	0.71	0.44
VO2AT (ml/Kg/min)					
Placebo	9.8 (3.1)		9.6 (3.2)		0.29
Liraglutide	10.0 (2.2)	0.41	10.0 (2.1)	0.61	0.97
Maximal heart rate (bpm)					
Placebo	140.6 (20.5)		145.2 (17.5)		0.25
Liraglutide	139.3 (23.5)	0.89	141.9 (22.2)	1.00	0.59
Maximal heart rate (%max)					

Placebo	83.8 (8.3)		86.8 (7.4)		0.22
Liraglutide	83.3 (11.5)	0.92	85.4 (14.5)	0.77	0.47
Resting Systolic Blood Pressure (mm Hg)					
Placebo	135.8 (20.8)		127.1 (12.6)		0.12
Liraglutide	130.7 (10.1)	0.54	125.5 (17.4)	0.80	0.34
Resting Diastolic Blood Pressure (mm Hg)					
Placebo	80.0 (12.0)		77.5 (12.2)		0.53
Liraglutide	78.2 (8.7)	0.69	74.1 (8.3)	0.69	0.20
Maximal Systolic Blood Pressure (mm Hg)					
Placebo	187.5 (32.2)		192.5 (25.6)		0.87
Liraglutide	179.6 (27.3)	0.52	171.7 (24.4)	0.045	0.18
Maximal Diastolic Blood Pressure (mm Hg)					
Placebo	86.7 (12.5)		87.9 (12.0)		0.86
Liraglutide	89.6 (13.7)	0.59	82.1 (10.5)	0.22	0.046
Maximal load (watt)					
Placebo	101.3 (50.5)		105.0 (52.7)		0.17
Liraglutide	109.2 (47.3)	0.84	108.2 (51.1)	0.74	0.30
RER max					
Placebo	1.22 (0.13)		1.23 (0.13)		0.77
Liraglutide	1.21 (0.13)	0.88	1.30 (0.12)	0.17	0.054

VE/VO2max					
Placebo	36.9 (5.3)		39.8 (8.2)		0.14
Liraglutide	37.0 (5.4)	0.97	40.0 (7.9)	0.96	0.27
VE/VCO2 slope					
Placebo	29.9 (8.2)		32.0 (4.5)		0.31
Liraglutide	29.8 (3.3)	0.35	30.2 (4.8)	0.36	0.81
VE/VCO2AT					
Placebo	30.9 (4.7)		32.1 (4.3)		0.09
Liraglutide	31.3 (3.5)	0.53	29.7 (2.4)	0.13	0.14
Heart rate recovery 1st minute (bpm)					
Placebo	20.8 (10.2)		22.8 (8.5)		0.31
Liraglutide	21.0 (9.5)	0.95	24.4 (10.2)	0.69	0.21
6 minute walk test					
Distance walked (m)					
Placebo	481.8 (92)		503.9 (84)		0.06
Liraglutide	504.8 (88)	0.54	530.7 (86)	0.45	0.023
Resting heart rate (bpm)					
Placebo	87.4 (16.5)		86.6 (16.2)		0.82
Liraglutide	78.6 (13.8)	0.17	81.6 (13.4)	0.42	0.20
6 min heart rate (bpm)					

Placebo	117.1 (18.8)		122.8 (19.7)		0.23
Liraglutide	116.9 (19.5)	0.18	121.1 (29.4)	0.87	0.39

440 VO2 max: maximal oxygen consumption. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. RER: Respiratory exchange ratio.
441 VE/VO2máx: ventilatory equivalent for oxygen (at the time of maximal oxygen consumption). VE/VCO2AT: ventilatory equivalent for carbon dioxide
442 (at the time of anaerobic threshold).

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445 **Table 3**: Echocardiographic findings at baseline and after 6 months' treatment

	Baseline	**p (vs placebo)**	**End of study**	**p (vs placebo)**	**p (vs baseline)**
Left Ventricular Ejection Fraction					
Placebo	0.64 (0.05)		0.66 (0.04)		0.32
Liraglutide	0.62 (0.07)	0.30	0.63 (0.06)	0.26	0.46
Left ventricular mass (g)					
Placebo	202 (63)		195 (56)		0.40
Liraglutide	225 (68)	0.27	221 (80)	0.35	0.33
Telediastolic ventricular diameter (mm)					
Placebo	46.7 (7.8)		49.1 (6.9)		0.14
Liraglutide	46.9 (6.4)	0.94	46.0 (6.0)	0.26	0.58
E-wave deacceleration time (ms)					
Placebo	227 (39)		207 (55)		0.26
Liraglutide	205 (34)	0.15	194 (37)	0.51	0.27
E/A					
Placebo	0.87 (0.28)		0.94 (0.28)		0.18

Liraglutide	0.94 (0.21)	0.27	0.90 (0.25)	0.66	0.48
Average E/e´					
Placebo	9.7 (2.6)		10.6 (3.9)		0.58
Liraglutide	8.8 (2.3)	0.49	10.0 (4.1)	0.75	0.19
Left Atrium diameter (mm)					
Placebo	39.4 (3.8)		40.7 (5.8)		0.33
Liraglutide	41.8 (5.8)	0.26	40.4 (4.6)	0.93	0.24

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447 **Table 4**: Glycaemic control and other safety variables

	Baseline	**p (vs placebo)**	**12 weeks**	**p (vs placebo)**	**End of study**	**p (vs placebo)**	**p (vs baseline)**
Fasting glucose (mg/dl)							
Placebo	189.9 (57.5)		181.2 (35.1)		158.2 (27.0)		0.083
Liraglutide	162.8 (26.4)	0.15	131.2 (36.9)	0.001	124.7 (22.0)	0.003	0.008
HbA1c (%)							
Placebo	8.4 (0.79)		8.2 (0.89)		7.7 (0.75)		0.012
Liraglutide	8.0 (0.46)	0.09	6.5 (0.73)	<0.005	6.7 (0.69)	0.002	<0.005
Insulin dose (IU/d)							
Placebo	16.4 (25.7)				19.4 (25.5)		0.11
Liraglutide	36.8 (86.0)	0.98			33.8 (84.9)	0.76	0.47
Insulin dose (IU/Kg.d)							
Placebo	0.18 (0.28)				0.21 (0.28)		0.063
Liraglutide	0.33 (0.70)	0.93			0.31 (0.68)	0.67	0.5
Patients with hypoglycaemia (N)							
Placebo			4		3		
Liraglutide			3	0.67	3	1.0	

C Peptide (ng/ml)							
Placebo	2.71 (0.91)				2.68 (1.02)		0.79
Liraglutide	2.90 (1.00)	0.65			2.90 (2.25)	0.77	0.99
Amylase (U/L)							
Placebo	57.4 (30.6)		58.5 (22.6)		55.5 (20.1)		0.21
Liraglutide	72.1 (33.0)	0.03	82.8 (34.3)	0.03	86.7 (34.0)	0.001	0.005
Lipase (U/L)							
Placebo	36.7 (36.3)		36.7 (22.6)		24.0 (9.4)		0.086
Liraglutide	42.6 (20.0)	0.14	63.1 (32.6)	0.01	58.9 (25.6)	0.001	0.03

448 To convert glucose to SI units (mmol/l), divide by 18; to convert C Peptide to nmol/l, multiply by 0.333

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451 **Table 5**: Anthropometry and other lab results

	Baseline	p (vs placebo)	End of study	p (vs placebo)	p (vs baseline)
Weight (Kg)					
Placebo	97.3 (14.8)		95.8 (14.8)		0.029
Liraglutide	93.2 (21.0)	0.59	88.3 (20.1)	0.31	0.001
BMI (Kg/m^2)					
Placebo	35.89 (5.96)		35.31 (5.68)		0.033
Liraglutide	34.07 (6.56)	0.49	32.25 (6.10)	0.078	0.001
Waist girth (cm)					
Placebo	114.2 (10.4)		112.5 (10.1)		0.19
Liraglutide	110.1 (12.7)	0.40	107.4 (14.1)	0.32	0.006
Total cholesterol (mg/dl)					
Placebo	196.6 (41.8)		187.8 (35.9)		0.16
Liraglutide	167.7 (27.4)	0.068	173.8 (50.9)	0.44	0.93
LDL cholesterol (mg/dl)					
Placebo	114.8 (28.7)		114.1 (29.0)		0.95
Liraglutide	91.7 (29.3)	0.059	101.6 (47.5)	0.45	0.60
HDL cholesterol (mg/dl)					
Placebo	50.8 (5.9)		49.5 (7.1)		0.25

Liraglutide	38.2 (7.5)	<0.005	40.9 (8.6)	0.014	0.10
Triglycerides (mg/dl)					
Placebo	156.3 (130.6)		121.2 (75.6)		0.083
Liraglutide	188.3 (55.0)	0.052	184.3 (100.9)	0.028	0.70
Apolipoprotein B (mg/dl)					
Placebo	105.0 (25.1)		96.5 (23.3)		0.12
Liraglutide	95.3 (15.2)	0.27	91.8 (26.5)	0.49	0.54
C-reactive Protein (mg/dl)					
Placebo	0.66 (0.30)		0.64 (0.30)		0.57
Liraglutide	0.37 (0.24)*	0.036	0.31 (0.29)*	0.017	0.99
NT-Pro-BNP (pg/ml)					
Placebo	38.3 (31.8)		41.3 (37.9)		0.68
Liraglutide	53.7 (43.8)	0.34	43.3 (52.7)	0.77	0.48

To convert cholesterol into mmol/l, multiply by 0.0256; to convert triglyceride into mmol/l, multiply by 0.0113; to convert apolipoprotein B to g/l, multiply by 0.01; to convert C-reactive Protein to nmol/l, multiply by 95.24; to convert NT-Pro-BNP to pmol/l, multiply by 0.1182.

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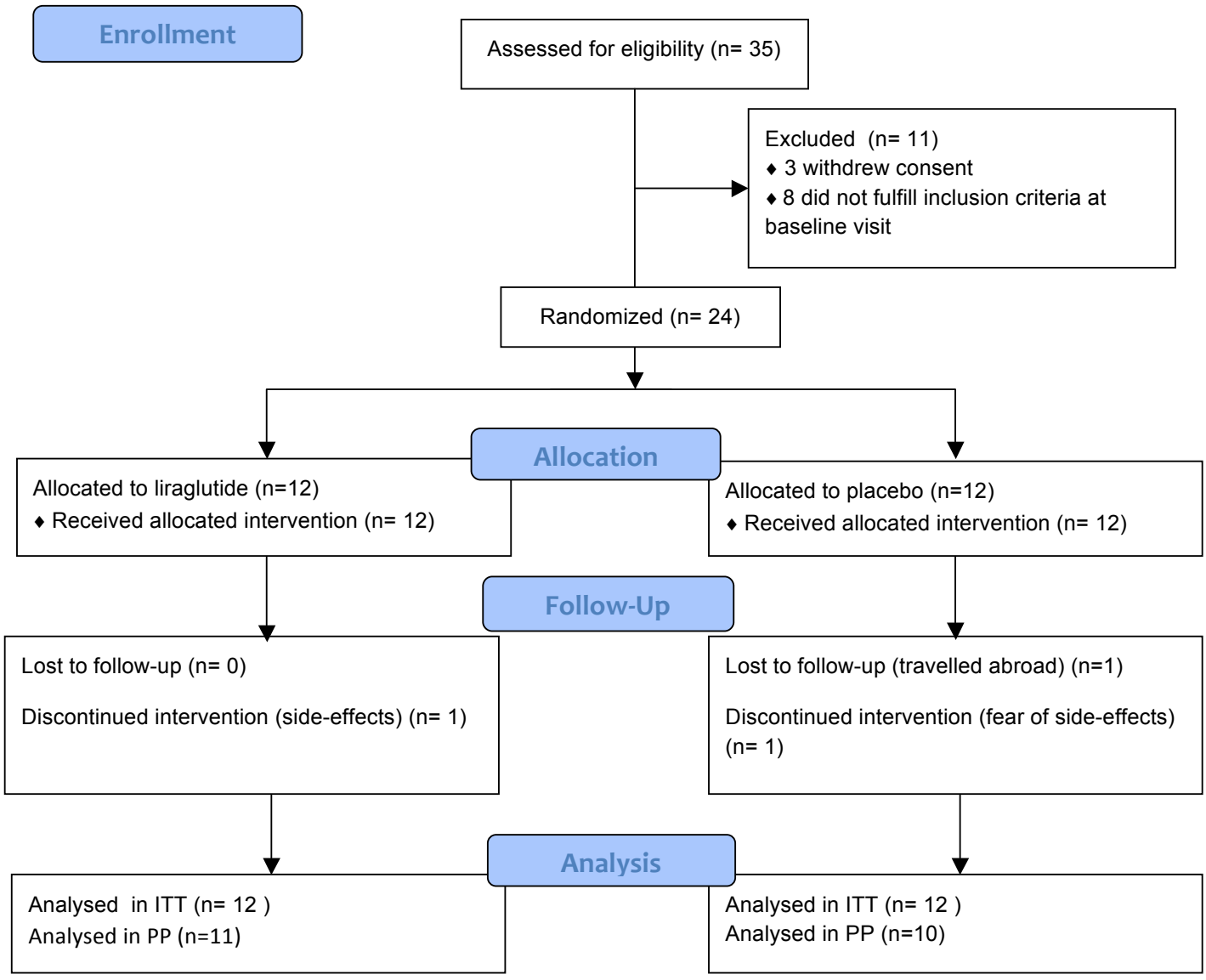
455 **Figure 1**: Participant flowchart.

Figure

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



Supplementary table 1: Compared treatment effects on echocardiografic outcomes

Echocardiogram	Baseline	End	Difference	Delta	P
Left ventricular ejection fraction					
Placebo	0,64 (0,04)	0,65 (0,04)	0.02 (-0.02, 0.05)	0.0005	0.985
Liraglutide	0,61 (0,07)	0,63 (0,06)	0.02 (-0.03, 0.06)	(-0.05, 0.55)	
Left ventricular mass (g)					
Placebo	202 (63)	195 (56)	-7.5 (-27.4, 12.4)	-4.16	0.792
Liraglutide	224 (68)	221 (80)	-3.3 (-31.2, 24.6)	(-36.67, 28.34)	
Left ventricle telediastolic diameter (mm)					
Placebo	46,7 (7,8)	49,05 (6,9)	2.37 (-0.94, 5.69)	3.32	0.155
Liraglutide	46,9 (6,4)	45,97 (6,0)	-0.94 (-4.62, 2.74)	(-1.35, 7.98)	

E-wave deacceleration time (ms)					
Placebo	227 (38)	207 (55)	-20.7 (-59.1, 17.6)	-9.33	0.647
Liraglutide	205 (34)	194 (37)	-11.4 (-33.2, 10.3)	(-51.56, 32.90)	
E/A					
Placebo	0,87 (0,28)	0,94 (0,28)	0.08 (-0.06, 0.22)	0.12	0.183
Liraglutide	0,94 (0,21)	0,90 (0,25)	-0.04 (-0.17, 0.08)	(-0.06, 0.29)	
Average E/e'					
Placebo	9,6 (2,6)	10,6 (3,9)	0.53 (-1.61, 2.67)	-0.67	0.382
Liraglutide	8,8 (2,3)	10,0 (4,1)	1.2 (-0.69, 3.10)	(-3.35, 2.00)	
Left atrium diameter (mm)					
Placebo	39,4 (3,8)	40,7 (5,8)	1.34 (-1.66, 4.33)	2.67	0.134
Liraglutide	41,7 (6,1)	40,4 (4,6)	-1.33 (-3.71, 1.05)	(-0.89, 6.23)	

Supplementary table 2: Side effects during the treatment period

	Placebo (12)	Liraglutide (12)
Gastrointestinal symptoms	3	12
Nausea/vomitting	2	6
Diarrhoea	1	1
Constipation	1	1
Heartburn/reflux		2
Abdominal discomfort/pain	1	6
Headaches	2	1
Infections	3	4
Upper respiratory tract/flu	2	3
Plantar wart	1	
Urinary tract infection		1
Neurologic symptoms		

Paresthesia	1	
Tremor	1	
Acute urinary retention		1
Dry mouth		1
Other		
Flushing		1
Atrial fibrillation		1
Asthaenia/weakness		1
Abnormal liver tests		1

Data Statement

Click here to download Data Statement: dataprofile.xml.pdf