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Heart rate variability in type 2 diabetic subjects randomized to liraglutide or glimepiride treatment, both in combination with metformin: A randomized, open, parallel-group study

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Summary

Aims: Reduced heart rate variability (HRV) and increased heart rate (HR) are associated with cardiovascular (CV) mortality. In the Liraglutide Effect and Action in Diabetes outcome trial, it was demonstrated a lower rate of CV events in type 2 diabetes (T2D) patients treated with liraglutide compared to placebo. We aimed to investigate the effects of liraglutide compared with glimepiride treatment in T2D patients on the CV risk parameters HR and HRV.

Methods: This was a post hoc study whereas sixty-two T2D individuals (45 males) were randomized to once daily 1.8 mg liraglutide or once daily 4 mg glimepiride, both in combination with 1 g metformin. HR and measurement of sympathetic activity, that is standard deviation (SD) of beat-to-beat (NN) intervals (SDNN), was assessed by 24-hour Holter monitoring system. Parasympathetic activity was analysed by root mean square of successive differences (RMSSD) in NN intervals and high-frequency (HF), low-frequency (LF) and very low-frequency power.

Results: Baseline clinical characteristics for liraglutide (n = 33) and glimepiride (n = 29) groups were well matched. There was a persistent increase in diurnal HR followed by a significantly increased HR at daytime 5.4 beats per minute, $P = 0.011$ in the liraglutide-treated group. There was no treatment change between groups in SDNN and RMSSD, or in HF and LF frequency power analysis.

Conclusions: Liraglutide treatment increased diurnal variation in hourly mean HR followed by an increase in mean daytime HR, independently of changes in sympathetic or parasympathetic activity.

KEYWORDS
automatic nervous system, cardiac autonomic neuropathy, glimepiride, heart rate variability, liraglutide, type 2 diabetes mellitus

1 | INTRODUCTION

Individuals with type 2 diabetes (T2D) have an increased risk of cardiovascular (CV) complications compared with the general population in which a multitude of risk factors for CV events are involved.[1] Multifactorial intervention against CV risk factors such as hyperlipidaemia, hypertension and hyperglycaemia has a sustained beneficial effect on CV complications.[2]

One overlooked diabetes complication is cardiovascular autonomic neuropathy (CAN).[3] Micro- and macrovascular complications resulting from CAN involve damage to the autonomic nerve fibres that innervate the heart and the vessels, which in turn may lead to dysfunctional heart rate (HR) control. A disorder of the automatic nervous system (ANS) reflects an imbalance between the sympathetic and the parasympathetic activity that can be assessed by measuring heart rate variability (HRV), that is the variation between two consecutive heartbeats; the higher the variation, the higher is the parasympathetic activity. Higher parasympathetic activity protects against CV events, whereas low HRV predicts CV events.[3]

It was demonstrated in the LEADER (Liraglutide Effect and Action in Diabetes) trial that the time-to-event analysis for the composite end-point, that is the rate of the first occurrence of CV death, nonfatal myocardial infarction or nonfatal stroke, was significantly lower among T2D patients treated with liraglutide compared with a placebo.[4] This effect was mainly driven by a significantly lower rate of CV death, while the mechanisms behind this remain elusive. In clinical trials, treatment with glucagon-like peptide-1 receptor agonist (GLP-1 RA) showed a small, however significant, increase in HR Preclinical and clinical experimental studies have demonstrated beneficial actions from GLP-1 RA activation on the vessels, heart and brain, independently of glycaemic control.[5]

GLP-1 RA may act on and change the activity of the ANS. This study aimed to investigate if liraglutide treatment, compared with glimepiride treatment, affects ANS in patients with T2D with subclinical heart failure.

2 | TRIAL DESIGN

This post hoc study was an open, assessor-blinded, randomized, controlled, parallel-group trial and a part of a larger study identified as NCT01425580 (www.clinicaltrials.gov). The main results of this study have been published elsewhere.[6]

Briefly, T2D patients who had glycated haemoglobin A1c (HbA1c) of 6.3% - 11% (45-97 mmol/mol) were eligible if they had not been previously treated with GLP-1 RA, dipeptidyl peptidase-4 inhibitors or glimepiride. Patients who met these criteria were invited for echocardiographic screening, in which one of the following criteria had to be fulfilled: left ventricle ejection fraction ≤50% or evidence of diastolic dysfunction. The major exclusion criteria were as follows: type 1 diabetes, treatment with glitazones during the previous 6 months, treatment with sulphonylureas in the previous 3 months, insulin treatment within the previous month, heart failure according to the New York Heart Association classification 3-4, past history of atrial fibrillation or flutter, presence of acute myocarditis or significant valvulopathies, uncontrolled hypertension, severe heart conduction disturbances or ventricular tachyarrhythmia within the previous 3 months, unstable angina or myocardial infarction in the previous 8 weeks, estimated glomerular filtration rate <30 mL/min, haemoglobin <90 g/L, BMI >40 kg/m^2, severe gastrointestinal disease, history of acute or chronic pancreatitis, malign neoplasia within the last 5 years, current drug or alcohol abuse and pregnancy.

Patients were block-randomized using sealed envelopes to receive either liraglutide or glimepiride during an 18-week treatment period. The initial dose of liraglutide was 0.6 mg (sc), with an up-titration of 0.6 mg every week to a final dose of 1.8 mg per day. The initial dose of the comparator was 2 mg glimepiride with an up-titration of 1 mg every week, reaching a final dose of 4 mg per day. The regional ethics committees at both participating centres reviewed and approved the trial protocol, and the study followed the International Conference on Harmonization–Good Clinical Practice guidelines. All subjects provided written informed consent before enrolment.

2.1 | Twenty-four-hour Holter monitoring (heart rate, heart rate variability and spectrum analysis)

Twenty-four-hour Holter monitoring (ambulatory electrocardiogram [ECG] recordings) was performed using Schiller Medilog AR12 Plus recorders (Schiller Medilog, Schiller AG, Baar, Switzerland). Three bipolar ECG leads (modified chest lead V1, V5 and aVF) were used. ECG data were extracted at baseline and after 18 weeks of treatment (liraglutide vs glimepiride).

The following parameters were calculated: for HR—mean, min/max, daytime (07:00 to 23:00) and midnight (24:00 to 6:00); for the time domain—mean beat-to-beat (NN) intervals, standard deviation of NN (SDNN), SD of the averages of NN intervals (SDANN) and SDNN of all 5-minutes segment recordings (SDNN index), square root of the mean squared difference (RMSSD) and percentage of adjacent NN intervals differing by more than 50 ms (pNN50%). The RMSSD and pNN50% are associated with parasympathetic activity, whereas SDNN is associated with sympathetic activity.

Fast Fourier spectrum analyses were performed to measure cardiac nervous system autonomic balance. The derived spectrum included bands of very low frequency (VLF; <0.04 Hz) and low frequency (LH; 0.04-0.15 Hz), that is an index of both sympathetic and parasympathetic activity, and high frequency (FH; 0.15-0.4 Hz), indicating the most efferent (parasympathetic) activity. Finally, index bands of the total power were calculated.

2.2 | Statistical analysis

Continuous data are presented as mean ± standard deviation (SD) or median with corresponding 1st quartile (Q1) and 3rd quartile (Q3), and categorical data are presented as percentages. Baseline

characteristics of patients were compared using Student's *t* test or the Mann-Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. For repeated measures, a generalized linear mixed model with random effects in patients and fixed effects of the time-period and treatment was used to compare the diurnal variation in hourly mean HR between groups. A generalized linear model was used to compare treatment changes in the 24-hour Holter monitoring parameters between groups. An intention-to-treat (ITT) analysis was performed with five imputations by using the iterative Markov chain Monte Carlo method for missing values in continuous variables.[7] A two-sided *P*-value of <0.05 was considered statistically significant. Data were analysed using IBM SPSS Statistics software, version 23.0 (IBM Corporation, Armonk, NY, USA) and Stata 15.1 (StataCorp, College Station, TX, USA).

3 | RESULTS

The CONSORT flow chart of the study is provided in Figure 1. One hundred and five patients were screened, while 43 of these were
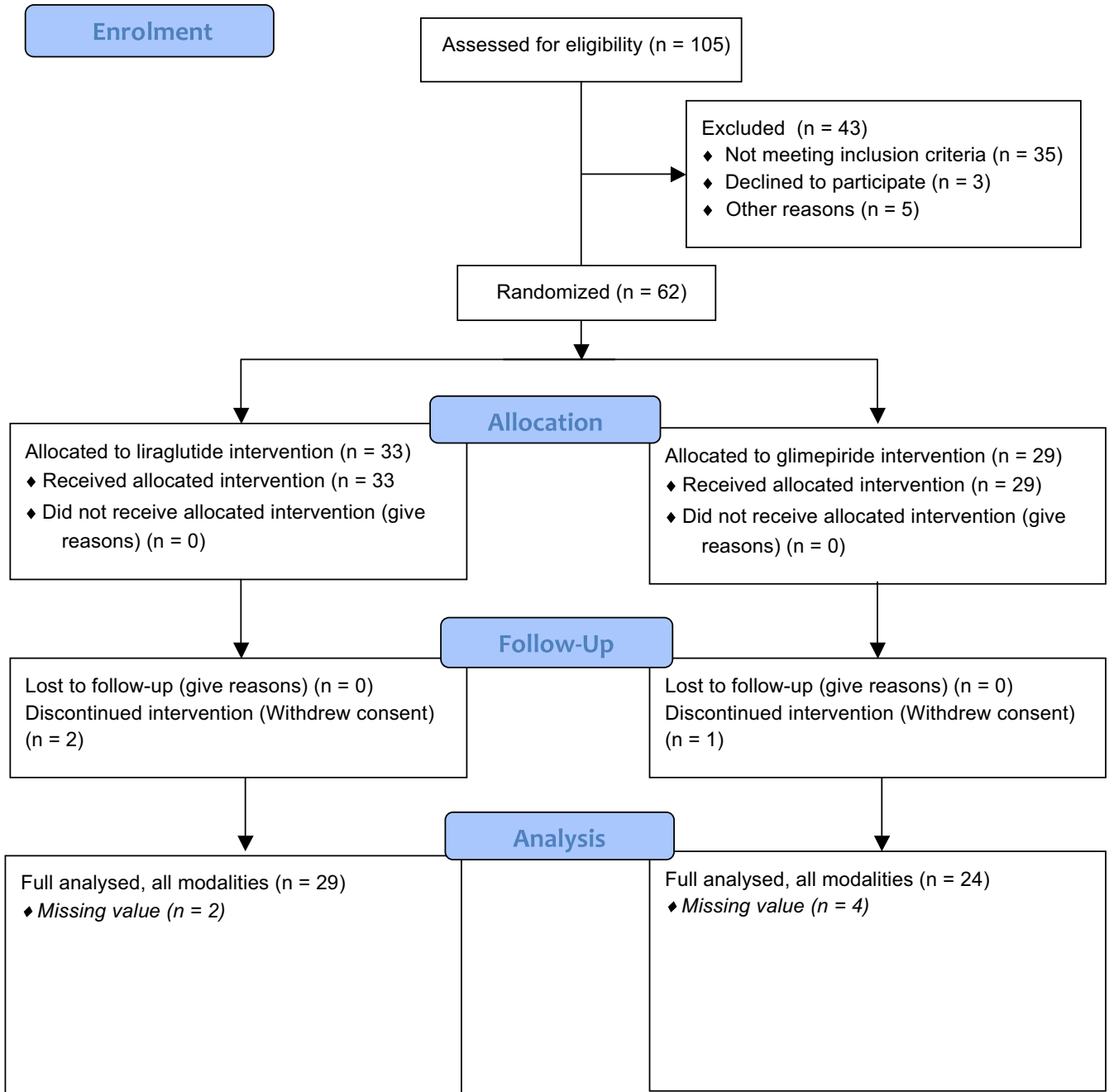

FIGURE 1 Flow chart for the study groups. 105 patients were screened, whereas 62 patients were eligible for the study, of these 33 vs 29 were randomized to liraglutide vs glimepiride, respectively. Due to technical hitches and dropouts, there were 29 in the liraglutide vs 24 in the glimepiride group, who were analysed per-protocol, that is full data set

TABLE 1 Baseline characteristics of the intention-to-treat population (ITT). Quantitative data are mean (±SD) or median (1st quartile, 3rd quartile), and categorical data are n (%)

	Liraglutide, n = 33	Glimepiride, n = 29	P-value
Age, year	60.8 ± 7.6	63.3 ± 6.8	0.240[a]
Male	24 (72.7%)	21 (72.4%)	1.000[b]
Diabetes duration, year	5 (1, 10)	3 (1, 7)	0.368[c]
Current smoker	3 (9.1%)	4 (13.8%)	0.852[b]
BMI kg/m^2	30.5 ± 4.4	29.0 ± 3.2	0.152[a]
Body weight, kg	92.8 ± 15.9	89.0 ± 9.9	0.411[a]
Waist circumference, cm	109.0 ± 13.0	106.3 ± 9.7	0.366[a]
Mean systolic BP, mm Hg	132 ± 14.0	129 ± 10.9	0.414[a]
Mean diastolic BP, mm Hg	77 ± 7.9	77 ± 7.9	0.838[a]
eGFR, mL/min/1.72m^2	88.3 ± 15.0	87.4 ± 13.1	0.799[a]
Complications			
Hypertension	29 (87.9%)	21 (72.4%)	0.224[b]
Hyperlipidaemia	25 (75.8%)	23 (79.31%)	0.980[b]
Coronary artery disease	10 (30.3%)	11 (37.9%)	0.714[b]
Stroke	1 (3.0%)	2 (6.9%)	0.902[b]
Proliferative retinopathy	1 (3.0%)	1 (3.45%)	1.000[b]
Treatment			
Antiplatelet therapy	11 (33.3%)	12 (41.4%)	0.696[b]
Anticoagulant therapy	3 (9.1%)	1 (3.5%)	0.714[b]
ACE inhibitors/ARB blockers	25 (75.8%)	20 (69.0%)	0.754[b]
Beta-blockers	14 (42.4%)	13 (44.8%)	1.000[b]
Calcium inhibitors	13 (39.4%0)	10 (34.5%)	0.894[b]
Diuretics	11 (33.3%)	6 (20.7%)	0.408[b]
Statins	22 (66.7%)	24 (82.8%)	0.248[b]
Biochemical parameters			
HbA1c, mmol/mol (IFCC)	54 (50, 60)	50 (49, 54)	0.036[c]
HbA1c, % (NGSP)	7.1 (6.7, 7.6)	6.7 (6.6, 7.1)	0.036[c]
Triglycerides, mmol/L	2.0 (1.4, 2.6)	1.5 (1.0, 2.2)	0.029[c]
Total cholesterol, mmol/L	4.4 (4.0, 6.0)	4.6 (3.7, 4.9)	0.530[c]
LDL-cholesterol, mmol/L	2.8 ± 1.2	2.5 ± 1.0	0.440[a]
HDL-cholesterol, mmol/L	1.1 ± 0.3	1.2 ± 0.3	0.417[a]

ARB, angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin A1c; HDL, high-density lipoprotein; IFCC, International Federation of Clinical Chemistry; LDL, low-density lipoprotein; NGSP, The National Glycohaemoglobin Standardization Program.

Quantitative data are mean ± standard deviation or median (first quartile, third quartile), and categorical data are n (%).

[a]Student's *t* test was used.

[b]Doubled one-sided *P*-value from Fisher's exact test.

[c]Mann-Whitney *U* test was used.

excluded owing to screening criteria (n = 35), declining to participate (n = 3) or other reasons (n = 5). Subsequently, 62 patients were randomized to liraglutide (n = 33) vs glimepiride (n = 29). There were none lost to follow-up; however, three patients withdrew their consent (Figure 1). For technical reasons (eg undetectable QRS segments in all three leads, high frequencies of ectopic complexes and distortions), another six patients were excluded from the per-protocol analysis. Finally, 29 patients in the liraglutide group and 24 in the glimepiride group made up the final analysis (per-protocol).

Sensitivity analysis (ITT analysis) was also carried out for our end-points.

There was a statistically significant but small difference in HbA1c and triglycerides observed between groups (Table 1). In the liraglutide-treated group, compared with the glimepiride-treated group, there was a statistically significant treatment change for reduction in weight −3.7 kg, 95% confidence interval (CI): −5.0 to −2.4 kg vs −0.2 kg, 95% CI: −1.9 to −1.5 kg; P = 0.001 and waist circumference −3.1 cm, 95% CI: −4.1 to −2.1 cm vs −0.8 cm, 95% CI: −2.5 to

TABLE 2 Effects of treatment change (baseline and at 18 weeks of treatment) for heart rate, heart variability and spectrum (frequency) analysis between groups treated with liraglutide vs glimepiride in combination with metformin

| | Liraglutide | | Glimepiride | | Treatment change | | | | | | |
	Baseline	18 weeks	Baseline	18 weeks	Liraglutide	n	Glimepiride	n	Effect difference	P-value	P-value[a]
HR parameter											
Mean HR (bpm)	71.2 ± 9.9	78.0 ± 9.4	69.9 ± 12.2	72.7 ± 12.9	7.6 ± 11.5	31	2.5 ± 10.1	28	5.1 (−0.6, 10.8)	0.079	0.096
Maximum HR (bpm)	126.8 ± 16.7	123.3 ± 17.2	129.5 ± 14.9	119.3 ± 18.5	−1.9 ± 15.9	30	−9.6 ± 19.8	28	7.6 (−1.8, 17.1)	0.111	0.114
Minimum HR (bpm)	55.2 ± 8.1	55.6 ± 9.2	53.0 ± 7.2	53.3 ± 7.2	0.4 ± 9.0	30	0.4 ± 6.4	28	−0.03 (−4.2, 4.1)	0.990	0.869
Daytime HR (bpm)	77.7 ± 9.1	83.2 ± 11.2	77.6 ± 9.5	77.9 ± 10.8	6.1 ± 8.3	30	0.8 ± 7.2	28	5.4 (1.3, 9.5)	0.011	0.023
Night-time HR (bpm)	75.4 ± 6.6	75.9 ± 11.5	73.6 ± 6.3	68.5 ± 9.4	0.6 ± 13.2	30	−5.2 ± 10.5	28	5.8 (−0.5, 12.1)	0.072	0.067
24-h time domain											
Log Mean NN (ms)	6.72 ± 0.16	6.73 ± 0.19	6.73 ± 0.16	6.75 ± 0.14	0.01 ± 0.14	32	0.01 ± 0.1	28	0 (−0.07, 0.06)	0.935	0.878
Log SDNN (ms)	4.50 ± 0.38	4.54 ± 0.41	4.69 ± 0.3	4.60 ± 0.28	0.04 ± 0.46	32	−0.08 ± 0.031	28	0.12 (−0.08, 0.33)	0.237	0.236
Log SDNNindex (ms)	3.63 ± 0.33	3.67 ± 0.59	3.70 ± 0.41	3.72 ± 0.4	0.02 ± 0.64	29	−0.01 ± 0.4	24	0.04 (−0.27, 0.34)	0.808	0.513
Log SDANN (ms)	4.32 ± 0.43	4.34 ± 0.41	4.53 ± 0.31	4.47 ± 0.28	0.01 ± 0.45	29	−0.04 ± 0.3	24	0.03 (−0.18, 0.25)	0.746	0.526
Log rMSSD (ms)	3.14 ± 0.56	3.20 ± 0.88	3.27 ± 0.65	3.21 ± 0.63	0.07 ± 1.03	32	−0.07 ± 0.61	27	0.14 (−0.31, 0.59)	0.536	0.502
Log pNN50 (%)	0.92 ± 1.17	1.00 ± 1.58	1.05 ± 1.31	1.04 ± 1.22	0.11 ± 1.66	32	−0.02 ± 1.13	28	0.12 (−0.62, 0.87)	0.741	0.688
Frequency domain											
Log LF (ms^2)	6.08 ± 0.87	5.91 ± 1.08	5.95 ± 0.75	5.92 ± 0.76	−0.20 ± 1.18	30	−0.16 ± 0.74	24	−0.04 (−0.59, 0.52)	0.889	0.903
Log HF (ms^2)	4.75 ± 1.15	4.65 ± 1.45	4.72 ± 0.81	4.78 ± 1	−0.13 ± 1.6	30	−0.09 ± 1.0	24	−0.04 (−0.79, 0.71)	0.916	0.967
Log VLF (ms^2)	7.47 ± 1.15	7.18 ± 1.18	7.40 ± 0.94	7.34 ± 0.82	−0.28 ± 1.11	30	−0.12 ± 0.61	24	−0.17 (−0.67, 0.34)	0.516	0.902
Log Total power (ms^2)	7.85 ± 1.08	7.56 ± 1.15	7.71 ± 0.86	7.69 ± 0.76	−0.29 ± 1.05	30	−0.10 ± 0.57	24	−0.19 (−0.67, 0.29)	0.427	0.781

General linear regression model was used for comparing effect difference.

[a]P-values of ITT analysis. Missing values were imputed using multiple imputation method and five imputed data sets were used for analyses.
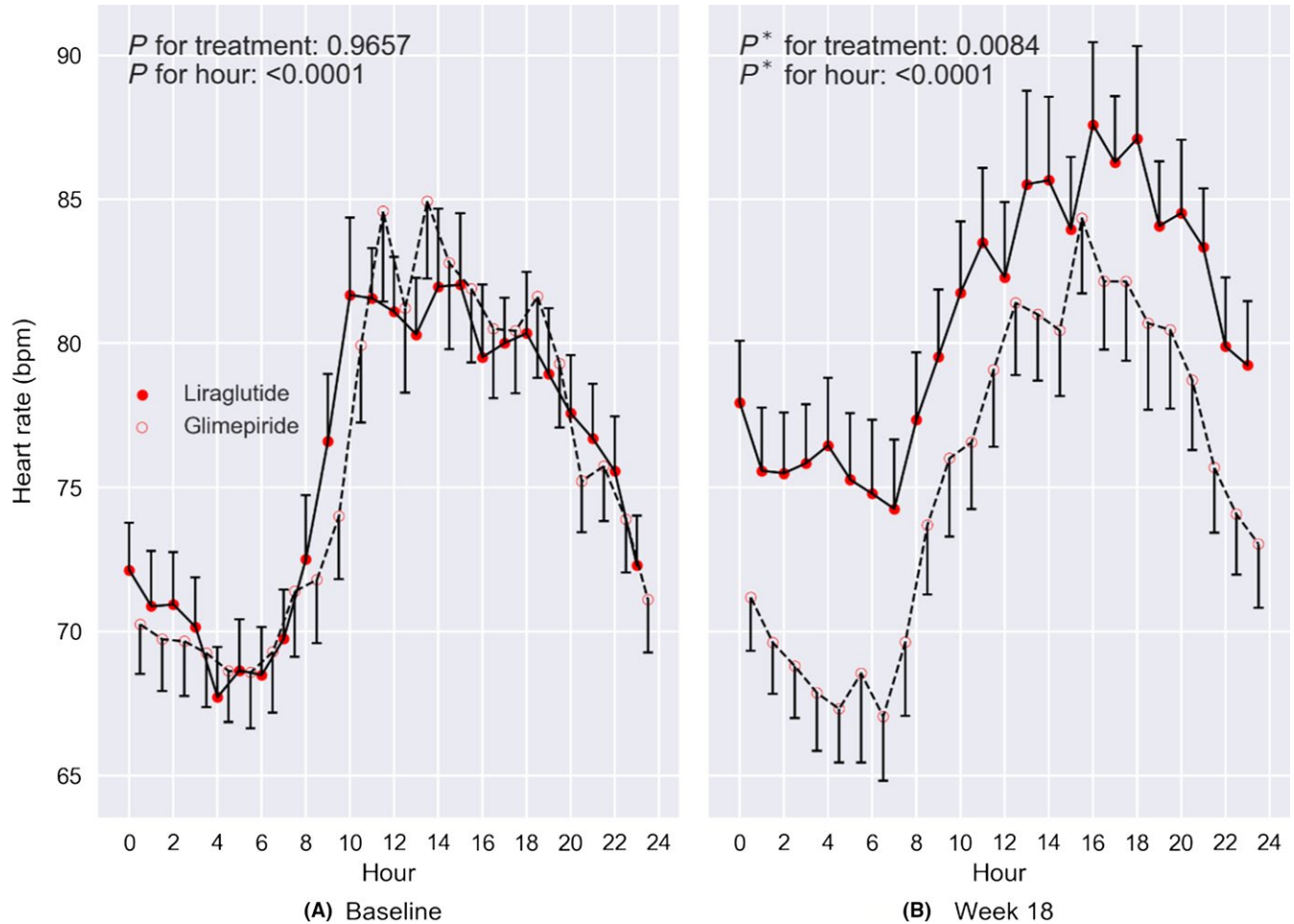
FIGURE 2 Diurnal variation in hourly mean HR between groups (liraglutide vs glimepiride). Error bars indicate mean ± standard error. Generalized linear mixed model for repeated measures was used to test the difference between the two groups. P^* is P-value adjusted for baseline heart rate. BPM; Beats per minute

−0.9 cm; $P = 0.019$, respectively. No such treatment change was observed for HbA1c −1.2%, 95% CI: −1.4 to −0.8% (−11.2 mmol/mol, 95% CI: −14.1 to −8.4 mmol/mol) vs −0.9%, 95% CI: −1.3 to −0.5% (−9.0 mmol/mol, 95% CI: −13.2 to −4.9 mmol/mol; $P = 0.37$) between groups.[6]

3.1 | Heart rate, heart rate variability and spectrum analysis (Fourier)

All data on HR, HRV and spectrum analysis are presented in Table 2. Depending on modalities and missing data from pre- and post-treatment 24-hour Holter recordings and owing to technical reasons (see above), there were 53 individuals (Table 2 and Figure 1) included in the final analysis (per-protocol).

At 18 weeks of treatment, there was a persistent increase in diurnal variation in hourly mean HR observed in the liraglutide-treated group (Figure 2). There was an increased mean HR at daytime in the liraglutide-treated group compared with the glimepiride-treated group (Table 2). There was a trend for an increased mean HR at nighttime ($P = 0.072$) and for the 24-hour period ($P = 0.079$) observed in the liraglutide-treated group compared with the glimepiride-treated

group (Table 2). Sensitivity analysis (ITT analysis) did not change the results (Table 2).

In the 24-hour time domain HRV, there were no statistically significant difference in treatment changes observed between groups for any of our variables, that is mean NN, SDDN, SDNN index, SDANN or pNN50% (Table 2). This non-significant treatment changes were also demonstrated in the ITT analysis (Table 2).

In the spectrum analysis (Fourier), which can reveal changes between sympathetic and parasympathetic activity, no statistically significant treatment change for any of the frequency domain variables, that is VLF, LF, HF and total power were observed between groups (Table 2). ITT analysis did not change the results.

Since there were significant treatment changes in parameters that may have affected ANS balance, that is glycaemic control, weight and blood pressure, we further did a simple regression analysis between on the one hand HbA1c, systolic BP, diastolic BP and weight, and on the other hand mean HR and SDNN. Coefficient of regression among these parameters and variables of HR, HRV and spectrum analysis is presented in Table 3. In the liraglutide group, there were statistically significant association between treatment changes in mean NN ($P = 0.006$) and weight ($P = 0.019$) against

TABLE 3 Regression coefficients (β) R^2 values and P-values from linear regression analysis[a] between treatment change (liraglutide vs glimepiride) for dependent and independent variables

Dependent variable	Independent variable	Liraglutide			Glimepiride		
		β	R^2	P-value	β	R^2	P-value
ΔHR	ΔHbA1c	−0.353	0.060	0.216	0.084	0.012	0.778
ΔHR	ΔWeight	−0.190	0.016	0.780	−0.130	0.007	0.810
ΔHR	ΔsBP	−0.056	0.010	0.703	−0.022	0.005	0.915
ΔHR	ΔdBP	−0.135	0.011	0.591	−0.046	0.022	0.839
ΔSDNN	Δmean NN	0.202	0.231	0.006	−0.002	0.000	0.980
ΔSDNN	ΔHbA1c	0.454	0.006	0.724	−0.604	0.017	0.450
ΔSDNN	ΔWeight	5.181	0.113	0.019	−2.444	0.065	0.081
ΔRMSSD	ΔHF	0.070	0.747	0.000	0.063	0.365	0.000
ΔRMSSD	ΔLF	0.048	0.589	0.000	0.033	0.276	0.015

[a]R^2 and P-values of ITT analysis. Missing values were imputed using multiple imputation method and five imputed data sets were used for analyses.

SDNN; and a statistically significant association between treatment changes in LF ($P < 0.001$) and HF ($P < 0.001$) against RMSSD (Table 3). For the glimepiride group, there was only a significant correlation between treatment changes in LF ($P = 0.015$) and HF ($P < 0.001$) against RMSSD (Table 3).

4 | DISCUSSION

In this open parallel study where T2D patients with subclinical heart failure were randomized to an 18-week treatment period with liraglutide vs glimepiride in combination with metformin, we investigated treatment changes in mean HR and HRV by using 24-hour Holter monitoring and spectrum analysis. At 18 weeks of liraglutide treatment, there was a persistent increased diurnal variation in hourly mean HR followed by an increase in mean HR daytime, compared with the glimepiride-treated group. Between groups, there was no treatment change in the ANS suggesting no involvement from sympathetic or parasympathetic tonus.

In clinical trials, different GLP-1 RA treatments, compared with placebo, have repeatedly demonstrated a small however significant increase in HR concomitant with a small reduction in blood pressure.[4,8-10] Mechanisms behind these observations remain elusive. Earlier studies in rodents have conclusively demonstrated that GLP-1 R activation increases blood pressure and HR by different routes, that is peripheral and central nervous system.[11] GLP-1 R is expressed at a high level in the area postrema and nucleus tractus solitarius, areas in the brain known for the central regulation of blood pressure and HR[12,13] Findings in rodents support a dual role of GLP-1 R activation on blood pressure and HR; on the one hand dependent on parasympathetic transmission from the central nervous system,[13,14] and on the other hand regulated by peripheral nervous structures by adrenergic and non-adrenergic stimulation.[11] This contrast clinical studies where a small reduction in blood pressure with a reciprocal small increase in HR frequently is reported[4,8-10] and suggested to be secondarily to vasodilatation, that is reflex tachycardia.[15] However,

recent reports have revealed GLP-1 R expression in the heart only by the sinoatrial node (SAN) myocytes,[16] whereas GLP-1 RA treatment directly may stimulate SAN to increase HR[17,18]

In the present study, we confirm previous observations, demonstrating an increase in HR due to liraglutide treatment. Patients treated with liraglutide had a persistent increased diurnal variation in hourly mean HR followed by a significant increase in HR for the daytime period although trended for increased mean HR night-time and during the 24-hour period. Since no significant treatment changes were observed at night-time, it suggests a relative sympathetic enhancement, rather than inhibition of parasympathetic activity (more predominant night-time). Notwithstanding this, there was no treatment change between groups in any of the HRV variables, nor in the high-frequency analysis; therefore, it seems unlikely that changes in the sympathetic or the parasympathetic system can explain the increased HR demonstrated in the liraglutide-treated group.

There was a treatment change for the reduction in weight in the liraglutide-treated group and a robust reduction in HbA1c in both groups. This confirms the well-characterized actions from GLP-1 RA treatment.[4,8-10] Not only activation of SAN may give explanation for the increased HR evoked by GLP-1 RA treatment. Also, expression of GLP-1 R in the vasculature supports a physiological role of GLP-1 R activation.[19] Therefore, modulation of ANS balance and reflex tachycardia in response to vasodilation is another suggestion for the increased HR observed by GLP-1 RA treatment. In the LEADER study, patients randomized to liraglutide had their blood pressure slightly decreased concomitant with a small increase in HR[4] This may reflect a reciprocal situation where decreased blood pressure may increase HR In the present study, at 18 weeks treatment, no effect on blood pressure was observed. In contrast, there was a transient (after 2 weeks treatment) increased diastolic blood pressure in the liraglutide-treated group (data published elsewhere).[20] In simple regression analysis, no correlation was observed between treatment change in blood pressure and treatment change in HR This suggests other mechanisms than reflex tachycardia behind the increased HR evoked by liraglutide treatment.

There is an increased risk of premature CV death with more rapid HR[21,22] Also, low HRV, reflecting an imbalance in ANS, is a predictor of CV events.[23] Despite a small, however significant, increase in HR in the large GLP-1 RA CV outcome studies patients treated with GLP-1 RA are not at higher risk of CV death compared with placebo.[4,8-10] In fact, in the LEADER study, patients treated with liraglutide were at lower risk for CV death compared with patients treated with placebo.[4] Recently, it was demonstrated in newly diagnosed overweight T2D patients treated with liraglutide an increased HR concomitant with a reduction in HRV (increased nightly HR and decreased parasympathetic activity). This effect was independent of weight loss and any improvement in glycaemic control and suggested to be due to changes in sympathovagal balance.[24] This contrasts to the present study results; although the increase in HR was much the same, we were not able to demonstrate any treatment change in the ANS balance (HRV or spectrum analysis). We cannot exclude that differences in diabetes duration, treatment duration, trial design or comorbidities may explain the difference between studies. One major difference between studies was that patients in the present study were diagnosed with subclinical heart failure (inclusion criteria) and therefore at high risk for CAN.[25] Therefore, our findings cannot be generalized to other than patients with T2D with subclinical heart failure.

Previous studies suggest that GLP-1 RA directly may activate SAN myocytes and increases HR[26] Although receptors for GLP-1 only are expressed by SAN myocytes, there is body of evidence demonstrating physiological action on the heart from GLP-1 R activation.[5] Some of these actions may be mediated through both GLP-1 R-dependent and GLP-1 R-independent pathways[27]; however, different actions by different GLP-1 RA may also contribute to varying results.[18] T2D patients treated with different GLP-1 RA had an increase in HR (acute and after 12 weeks) that was not explained by changes in sympathetic activity, or a reflex to vasodilation, suggesting direct stimulation of SAN involved.[18] Acute administration of exenatide into healthy overweight men[17] and into T2D patients with heart failure[28] increased HR that not was due to reflex tachycardia, however rather to the involvement of sympathetic action or stimulation of SAN. In another recent study where T2D patients received exenatide extended-release, there was an increase in HR that did not appear to be related to sympathetic influence.[29] In a current study, simple regression analysis revealed a significant correlation between treatment change in mean NN and weight against changes in SDNN in the liraglutide-treated group, compared with the glimepiride-treated group. Correlations were also demonstrated between changes in LF and HF against change in RMSSD in both groups. Despite this, there was no treatment change in any of the ANS parameters between groups, nor were there any treatment changes in the spectrum analysis parameters between groups. This supports (more than any plausible explanation of why liraglutide increases HR) the already known associations between changes in metabolic parameters and spectrum analysis parameters against changes in HRV parameters.

The limitations of this study include its open-label design, which may have introduced some biases between groups. However, patients were randomized to one of the treatment groups and data were analysed blinded to minimize further biases. At baseline, there was a small, however significant, higher HbA1c and triglycerides concentrations observed in the group allocated to liraglutide. Although, no treatment changes (after 18 weeks) were observed in these parameters between groups, we cannot entirely role out that this difference might have affected our outcome. As the comparator group were treated with glimepiride, the possibility of hypoglycaemia-induced tachycardia has to be considered. However, there was no severe hypoglycaemic event during the study (no groups) although a numerical (non-significant) higher numbers of mild hypoglycaemia in the glimepiride group was observed.[6] Despite this HR was not increased in patients treated with glimepiride compared to patients treated with liraglutide, making this consideration less important. Because of dropouts and technical hitches, full data were available for 85% of the study population (53 out of 62) and subsequently analysed per-protocol. After multiple imputations and sensitivity analysis, the results were not changed, supporting the per-protocol results.

Eighteen-week treatment with liraglutide, compared with glimepiride, in combination with metformin significantly increased diurnal variation in hourly mean HR followed by an increase in mean daytime HR, with no effects on HRV. Increased HR induced by liraglutide treatment is suggested to be independent from sympathetic or parasympathetic involvement. Further studies are warranted to elucidate the mechanisms behind the increased HR observed with GLP-1 RA treatment.

CONFLICT OF INTEREST

AUTHORS' CONTRIBUTION

AVAILABILITY OF THE DATA AND MATERIAL

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