JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2021, 72, 5, 751-761
www.jpp.krakow.pl | DOI: 10.26402/jpp.2021.5.10

M. WAJDLICH, M. NOWICKI

HEMODYNAMIC EFFECT OF A SINGLE DOSE OF GLUCAGON-LIKE PEPTIDE 1 RECEPTOR (GLP-1R) AGONIST LIRAGLUTIDE IN PATIENTS WITH DIABETIC KIDNEY DISEASE

Department of Nephrology, Hypertension and Kidney Transplantation,
Central University Hospital, Medical University of Lodz, Lodz, Poland

Increased peripheral resistance and autonomic nervous system is a key link in pathogenesis of arterial hypertension in diabetic kidney disease. Net effect of glucagon-like peptide 1 receptor (GLP-1R) agonists on blood pressure may result from interplay between vasodilatation, increased natriuresis, heart rate and sympathetic nervous system activity. The aim of study was to compare hemodynamic effect of single subcutaneous dose of 1.2 mg liraglutide to placebo in patients with type 2 *diabetes mellitus* and impaired renal function. This cross-over study included 17 patients with estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2 and 17 patients with eGFR > 60 ml/min/1.73 m^2. Blood pressure and heart rate were monitored for 24 hours after liraglutide or placebo. Before and after each medication, systemic vascular resistance, heart rate variability, pulse wave velocity and central blood pressure were measured. Significant increases of 24 h mean heart rate and cardiac output were seen in both groups. Sympathetic predominance was observed in patients with eGFR < 30 ml/min/1.73 m^2 after GLP-1R agonist compared to placebo ($p = 0.005$). Systemic vascular resistance decreased after liraglutide compared with placebo only in patients with eGFR > 60 ml/min/1.73 m^2 ($p = 0.002$), whereas pulse wave velocity increased after liraglutide compared with placebo only in patients with eGFR < 30 ml/min/1.73 m^2 ($p = 0.0006$). The 24 h mean arterial pressure after liraglutide significantly increased compared to placebo only in latter group. Liraglutide administration in patients with advanced chronic kidney disease (CKD) induces increase of blood pressure due to increase of cardiac output secondary to acceleration of heart rate associated with sympathetic predominance. The vasodilatory effect of liraglutide is preserved only in earlier CKD.

Key words: *diabetic kidney disease, glucagon-like peptide 1 receptor agonists, liraglutide, blood pressure, cardiac output, glomerular filtration rate, chronic kidney disease*

INTRODUCTION

Diabetes mellitus (DM) is one of the common chronic diseases associated with increased long-term failure of various organs, including diabetic nephropathy. The conclusions of some studies e.g. about the protective role of the rs3134069 polymorphism in chronic kidney disease (CKD) development in patients with type 2 *diabetes mellitus* (1) or about the potential reno-protective effect of galangin in the experimental studies (2) are very promising. Nevertheless, diabetic nephropathy is considered a major cause of CKD and still contributes to excess morbidity and mortality among the diabetic population.

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have recently emerged as a new treatment option in patients with type 2 diabetes mellitus since they may reduce not only glycated hemoglobin (HbA1c) but also induce weight loss (3) and reduce cardiovascular risk (4). The GLP-1 receptor agonists reduced major adverse cardiac events (MACE) by 14% (HR 0.86 [95% CI 0.80 – 0.93]; p < 0·0001), all-cause mortality by 12% (HR 0.88 [95% CI 0.82 – 0.94]; p = 0·0001), hospital admission for heart failure by 11% (HR 0.89 [95% CI 0.82 – 0.98]; p = 0.013), and the composite kidney outcome by 21% (HR 0.79 [95% CI 0.73 – 0.87]; p < 0·0001) according to most previous metanalysis (5). Moreover in the AMPLITUDE O study, involving 31.6% participants with type 2 diabetes and current kidney disease (defined as an estimated glomerular filtration rate of 25.0 to 59.9 ml per minute per 1.73 m^2 of body-surface area), the risk of cardiovascular events was lower among those who received weekly subcutaneous injections of efpeglenatide. MACE occurred in 7.0% participants assigned to receive GLP-1R agonist and 9.2% assigned to receive placebo (hazard ratio, 0.73; 95% confidence interval [CI], 0.58 to 0.92; p < 0.001 for noninferiority; p = 0.007 for superiority) (6). Hence, the GLP-1 agonists could be good therapeutic option especially for the patients with diabetic kidney disease (DKD), considering the more advanced kidney disease stages as a special point of interest, because of the highest risk of cardiovascular events and development of heart failure. However the data about potential impact of GLP-1 receptor agonists on the cardiovascular system in this group are limited.

Arterial hypertension has been recognized as a main risk factor for cardiovascular events and is highly prevalent in patients with DKD (7). The complex pathogenesis of arterial

hypertension in DKD may often hinder an optimal blood pressure control in this group of patients. It has been suggested that GLP-1 receptor agonists (GLP-1RA) may possess a blood pressure lowering effect. The meta-analysis of six trials of liraglutide showed a mean systolic blood pressure (SBP) reduction of 2.5 mmHg within 2 weeks of treatment (8). GLP-1 mimetics may modulate multiple pathways of blood pressure regulation (*Fig. 1*) (9). The improvement of vascular function has been found both *ex vivo*, in pre-constricted pulmonary arteries (10), and *in vivo* in salt-sensitive hypertensive rats (11), healthy humans (12), and subjects with type 2 diabetes (13). GLP-1 agonists may also induce natriuresis and diuresis through the inhibition of the sodium-hydrogen exchanger 3 (NHE3) localized at the brush border of the renal proximal tubular cells (14, 15).

Several recent systematic reviews and metanalyses of clinical trials confirmed that administration of a GLP-1R agonist was associated with modest reduction of blood pressure at expense of a slight increase of heart rate (16-18). Although improvement in glucose metabolic parameters have been associated with improvement of heart rate variability (HRV) (19), some studies showed that GLP-1 and GLP-1 RAs may also directly decrease HRV (20). It is unclear whether increased heart rate and sympathetic activity seen during the GLP-1 RA therapy might adversely affect the safety of the GLP-1 agonist therapy (21) expecially in more advanced kidney failure.

The increased peripheral resistance resulting from the imbalance of factors that modulate vascular tone and autonomic nervous system activity is important for the pathogenesis of arterial hypertension in diabetic kidney disease (22). The potential mechanisms of peripheral vascular dysfunction caused by CKD include increased oxidative stress, L-arginine deficiency, elevated plasma levels of asymmetric dimethylarginine (ADMA), impaired nitric oxide bioavailability as well as an accelerated atherosclerosis and calcification (23). The mechanisms leading to sympathetic hyperactivity in CKD seem to be complex and multifactorial. Kidney injury may enhance sympathetic nerve activity (24) and the kidneys secrete the enzymes that retard catecholamine metabolism including monoamine oxidase, methyltransferase and renalase (25).

The aim of the study was to investigate the hemodynamic effect of a single subcutaneous dose of liraglutide compared to placebo in patients with type 2 *diabetes mellitus* and either moderately or severely impaired kidney function.

MATERIALS AND METHODS

Patients and methods

All patients provided written informed consent before the start of study procedures. The local ethics committee approved study protocol. The trial was conducted in compliance with Good Clinical Practice Guidelines and ethical principles stated in the Declaration of Helsinki.

The prospective single-dose cross-over double-blind placebo-controlled study included 34 patients divided into two subgroups with different degrees of renal function impairment, i.e. with estimated glomerular filtration rate (eGFR) below 30 ml/min/1.73 m^2 (n = 17) and above 60 ml/min/1.73 m^2 (n = 17). Glomerular filtration rate was calculated using CKD-EPI equation.

The doses of chronic antihyperglycemic and antihypertensive medications as well as diuretics had not been modified for at least one month before study and chronic medications were continued in unchanged dose during the study. The meal plan and total daily fluid intake as well as physical activity were kept constant during the study. The baseline characteristics of the study group are presented in *Table 1*.

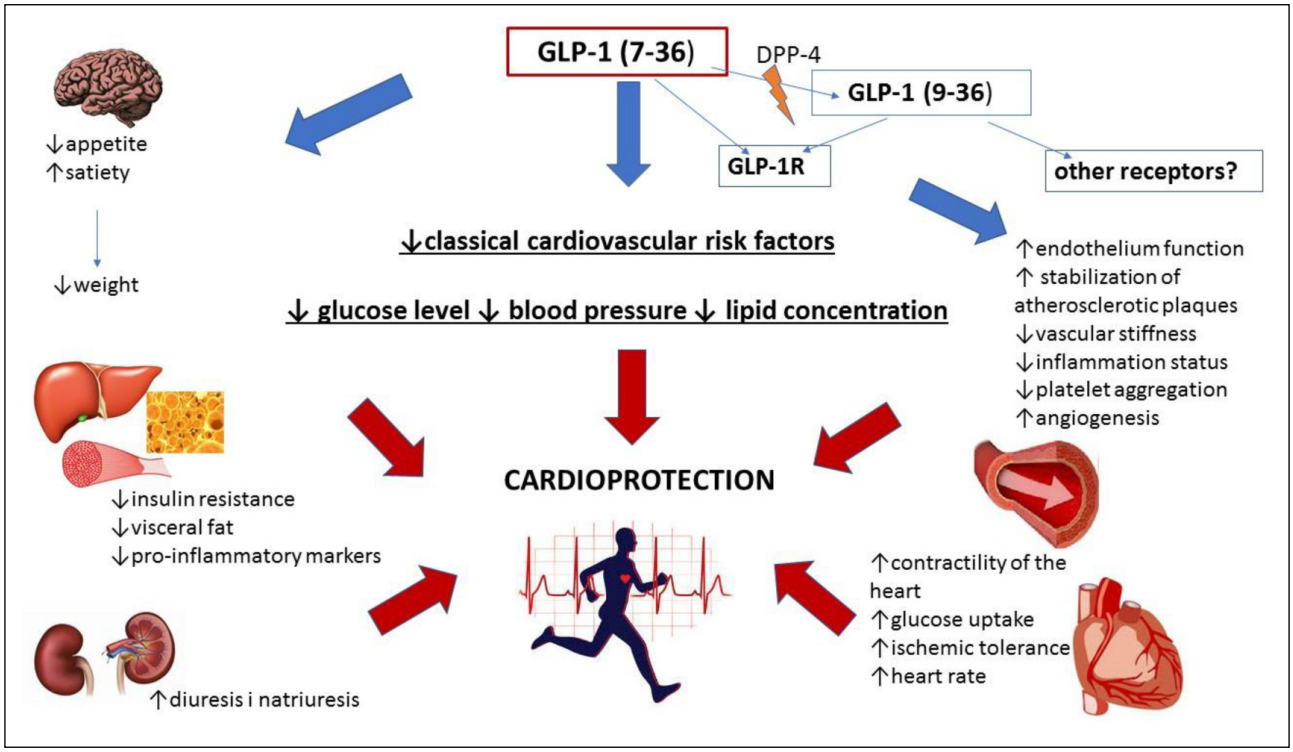

Fig. 1. Cardioprotective impact of glucagon-like peptide 1 (GLP-1) and GLP-1 agonists.

Table 1. Baseline characteristics of patients with estimated glomerular filtration rate (eGFR) > 60 and < 30 ml/min/1.73m^2.

	eGFR < 30 ml/min/1.73m^2	**eGFR > 60** ml/min/1.73m^2	**p-value**
Mean eGFR (ml/min/1,73m^2)[1]	25.1 ± 3.4	65.6 ± 4.6	<0.0001
Age (years)[1]	68 ± 6	64 ± 9	0.2
Sex (F-female, M-male)	F 29.4% (n = 5) M 70.6% (n = 12)	F 64.7% (n = 11) M 35.3% (n = 6)	0.04
BMI (kg/m^2)[1]	32.1 ± 3.9	31.3 ± 6	0.05
Duration of diabetes (years)[1]	16 ± 5	10 ± 4	0.001
Insulin therapy (%)	88.2% (n = 15)	29.4% (n = 5)	0.0005
HbA1c (%)[2]	7.3 (5.9 – 9.7)	6.8 (5.8 – 8.2)	0.005
Ischemic heart disease (%)	94.1% (n = 16)	64.7% (n = 11)	0.03
History of cardiovascular events (%)	47% (n = 8)	5.9% (n = 1)	0.02
History of smoking (%)	58.8% (n = 10)	17.7% (n = 3)	0.01
Time since diagnosis of hypertension (years)[2]	16 (10 – 20)	10 (8 – 15)	0.01
Median number of antihypertensive drugs[3]	4 (3 – 6)	4 (3 – 5)	0.01
ACE inhibitors	21.4% (5/17)	41.1% (7/17)	0.47
Angiotensin II receptor blockers	35.3% (6/17)	52.9% (9/17)	0.3
Aldosterone antagonists	0% (0/17)	5.9% (1/17)	0.3
Diuretics	100% (17/17)	88.2% (15/17)	0.14
Centrally-acting antihypertensives	17.7% (3/17)	23.5% (4/17)	0.67
SBP (mmHg)[1]	143 ± 14	132 ± 14	0.04
DBP (mmHg)[1]	75 ± 7	74 ± 8	0.74

1 mean ± standard deviation 2 median with interquartile range (IQR) 3 median with (min.-max) range
BMI, body mass index; HbA1c, glycated hemoglobin; ACE, angiotensin converting enzyme; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Each subject received a single subcutaneous dose of 1.2 mg liraglutide or placebo in a random order with 48-hour interval and subsequent clinical follow-up in metabolic ward, during which blood pressure was monitored for the following 24-hours and the hemodynamic parameters were non-invasively assessed.

Blood pressure was monitored with BR-102 plus ambulatory blood pressure monitoring (ABPM) system (Schiller, Baar, Switzerland). The device recorded blood pressure and heart rate in 15-minutes intervals during the day and 30-min intervals during the night. ABPM recordings were defined as valid with ≥ 70% readings. The diurnal periods, e.g. daytime activity and nighttime rest were determined from physical activity diaries filled by the patients. The basic hemodynamics parameters including Thoracic Fluid Index - inverse of baseline bioimpedance (TFI), Contractility Index (CI), Heart Rate (HR, bpm), Ventricular Ejection Time (VET, ms), Early Diastolic Filling Ratio (EDFR, %), that were used to compute the following parameters: Stroke Volume/Index (SV, ml), Cardiac Index (CI, l/min./m^2), Systemic Vascular Resistance/Systemic Vascular Resistance Indexed (SVR/SVRI, d.s/cm^5.m^2), Left Cardiac Work Index (LCWI, kg.m/m^2), Ejection Fraction (EF, %), End Diastolic Volume (EDV, ml) were assessed with bioimpedance cardiography (Physioflow Enduro, Manatec, France). The hemodynamic parameters were measured at two time points during each study day: immediately before and 11 hours after the study drug or placebo administration, i.e. at the expected Tmax of liraglutide (26).

At same time points central systolic blood pressure (cSBP), central pulse pressure (cPP), augmentation index (AI) and subendocardial viability ratio (SEVR) were measured with applanation tonometry by SphygmoCor® (v. 9.0, AtCor Medical®, Sydney, Australia). Pressure waveforms were recorded at carotid artery followed by radial artery, with simultaneous ECG signal recording.

The analysis of Heart Rate Variability (HRV) was performed 11 hours after the study drug or placebo. All measurements of all hemodynamic parameters were performed in a supine position, after 15-minute rest.

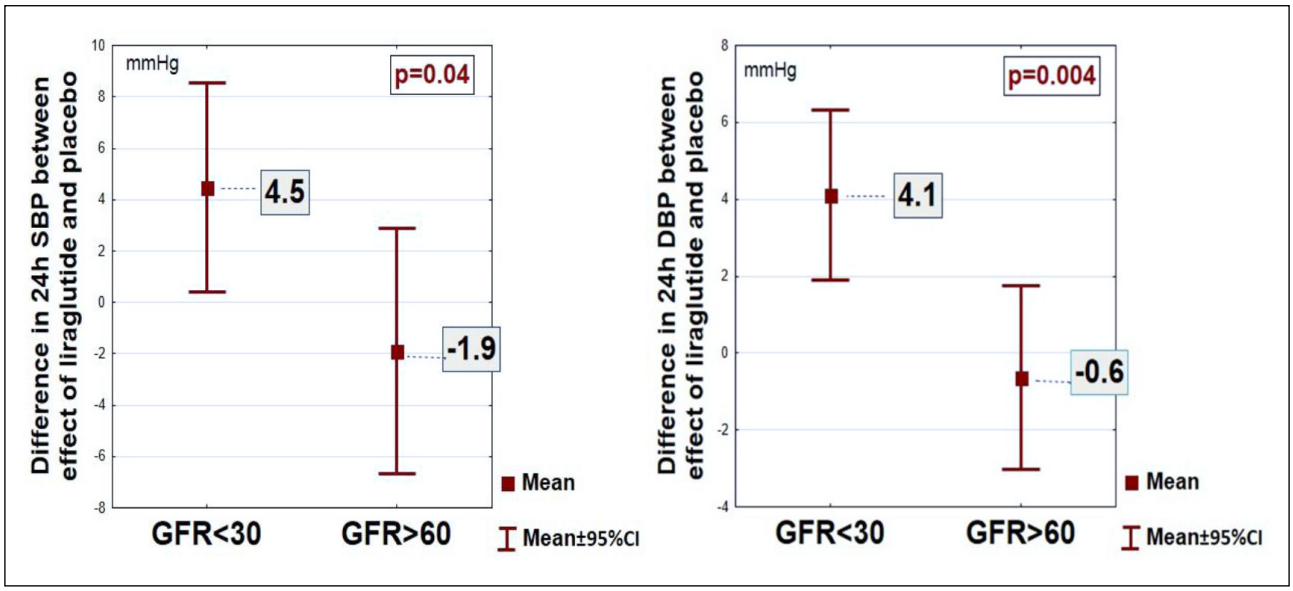

Fig. 2. Change of mean 24 h blood pressure after the administration of liraglutide corrected for placebo in patients with estimated glomerular filtration rate (eGFR) > 60 and < 30 ml/min/1.73m^2.

Statistical analysis was carried out with Statistica 13.1 PL software. Shapiro-Wilk test was used to check normality of variable distribution. A t-test for independent samples was used to compare means between two groups for normally distributed variables. Student's paired t-test was used to determine within group differences before and after drug or placebo administration. Chi^2 test was used to analyze categorical variables. For non-normally distributed variables the non-parametric tests were used, i.e. the Mann-Whitney U test for independent samples and the Wilcoxon signed rank test for paired samples. Pearson or Spearman correlation coefficient was calculated to assess association between variables depending on normality of their distribution. $p < 0.05$ was taken as statistically significant. The data are presented as mean ± SD or median and 25 – 75% interquartile range (IQR) depending on variable distribution. 95% Cl was calculated to present the changes of parameters after administration of study drug or placebo.

RESULTS

After administration of liraglutide 24-hour mean arterial pressure (MAP) was significantly higher than after placebo (102.4 ± 8.6 vs. 97.8 ± 8.1 mmHg, $p = 0.003$) in patients with eGFR < 30 ml/min/1.73 m^2. Baseline values of systolic and diastolic blood pressure on the day when placebo or liraglutide were administered did not differ significantly. Respective values of blood pressure were 141/83 mmHg and 139/83 mmHg before the administration of placebo and liraglutide, respectively. In the patients with eGFR > 60 ml/min/1.73 m^2 no significant difference of 24 h MAP was found between liraglutide and placebo (95.7 ± 8 mmHg vs. 97.2 ± 10.8, respectively, $p = 0.35$). The baseline values of systolic and diastolic blood pressure in placebo and liraglutide day did not also differ significantly (138/75 mmHg and 136/74 mmHg, respectively). *Fig. 2* displays the differences of mean systolic and diastolic blood pressure values derived from 24-hours recordings between liraglutide and placebo.

No significant changes of aortic blood pressure parameters were found in study groups except for AI and SEVR that significantly decreased after liraglutide compared to placebo only in patients with eGFR < 30 ml/min/1.73 m^2 (*Table 2*).

The significant increases of both 24 h mean heart rate and cardiac output were seen in both groups. In the patients with eGFR > 60 ml/min/1.73 m^2 mean 24 h heart rate was 73 ± 8 after liraglutide compared with 68 ± 5 beats per minute (bpm) after placebo ($p = 0.005$), whereas in patients with eGFR < 30 ml/min/1.73 m^2 the respective values were 76 ± 9 and 67 ± 9 bpm ($p < 0.001$) (*Table 3*). In the latter group a decrease of the parasympathetic system activity and sympathetic predominance was seen after the liraglutide injection (*Fig. 3*). The analysis of the frequency domain parameters showed a significant reduction of the normalized values of HF power and a significant increase in LF power and LF/HF ratio values after liraglutide compared to placebo in patients with eGFR < 30 ml/min/1.73 m^2. In the patients with eGFR > 60 ml/min/1.73 m^2 no significant difference of the autonomic system balance was revealed between liraglutide and placebo. The change of normalized values of LF power in spectral analysis correlated positively with the change of heart rate after liraglutide ($r = 0.36$, $p = 0.037$) whereas the change of HF power correlated negatively with the change of heart rate after liraglutide ($r = –0.39$, $p = 0.023$).

The hemodynamic parameters were similar at baseline before the administration of liraglutide and placebo in both groups. *Table 4* displays the mean change of hemodynamic parameters after the injection of liraglutide and placebo. The significant increase of cardiac output after liraglutide compared to placebo was noted in both study groups. In addition to the increase of cardiac output, the significant changes of early diastolic filling ratio and contractility index were found. The early diastolic filling ratio significantly increased after the injection of liraglutide vs. placebo in patients with eGFR < 30 ml/min/1.73 m^2 and contractility index was higher after liraglutide compared to placebo in patients with eGFR > 60 ml/min/1.73 m^2. *Table 5* shows the effects of liraglutide and placebo on the systemic vascular resistance in each group. The systemic vascular resistance decreased after the injection of liraglutide compared with placebo only in the patients with less impaired kidney function ($p = 0.002$), whereas the pulse wave velocity increased after liraglutide vs. placebo ($p = 0.0006$) only in the patients with eGFR < 30 ml/min/1.73 m^2 (*Fig. 4*).

Table 2. The changes of central blood pressure parameters after liraglutide or placebo in patients with estimated glomerular filtration rate (eGFR) > 60 and < 30 ml/min/1.73m^2.

Change of parameter after intervention (Δ)	**eGFR< 30 ml/min/1.73m^2**			**eGFR > 60 ml/min/1.73m^2**		
	Placebo	**Liraglutide**	**p** (liraglutide vs. placebo)	**Placebo**	**Liraglutide**	**p** (liraglutide vs. placebo)
AoSBP[2] (mmHg)	1[2] (–2) – (4)	0[2] (–6) – (8)	0.74	–2[2] (–4) – (3)	0[2] (–10) – (2)	0.55
AoPP[2] (mmHg)	–1.7[1] (–4) – (0.6)	0.5[1] (–3.9) – (4.8)	0.42	1.2[1] (–2.2) – (4.6)	–1.9[1] (–5.5) – (1.8)	0.25
AP (mmHg)	0.8[1] (–0.5) – (2.1)	–1.4[1] (–4.4) – (1.6)	0.15	0.6[1] (–0.95) – (2.1)	–0.6[1] (-3.0)-(1.8)	0.35
AIx (%)	2.9[1] (0.4) – (5.3)	-3.9[1] (–8.6) – (0.9)	**0.006**	0.9[1] (–2.6) – (4.4)	1.1[1] (–1.9) – (4.0)	0.93
AIx-HR75[1] (%)	0.8[1] (–2.3) – (3.9)	1.2[1] (–5) – (7.5)	0.87	0.2[1] (–2.8) – (3.3)	3.6[1] (0.8) – (6.5)	0.08
SEVR[1] (%)	2[2] (–3) – (3)	–12[2] (–32) – (1)	**0.006**	0[2] (–6) – (4)	–8[2] (–25) – (4)	0.06

1 mean, 95% confidence interval 2 median, 95% confidence interval
AoSBP, aoritc systolic blood pressure; AoPP, aortic pulse pressure; AP, augmentation pressure; AIx, augmentation index; AIx-HR75, augmentation index corrected for heart rate 75 bpm; SEVR, subendocardial viability ratio

Table 3. Mean heart rate (HR) after liraglutide or placebo in patients with eGFR > 60 and < 30 ml/min/1.73m^2.

eGFR < 30 ml/min/1.73m^2				**eGFR > 60 ml/min/1.73m^2**			
Parameter (bpm)	**Placebo**	**Liraglutide**	**p value**	**Parameter** (bpm)	**Placebo**	**Liraglutide**	**P value**
24 h HR[1]	67 ± 9	76 ± 9	**p < 0.001**	**24h HR**[1]	68 ± 5	73 ± 8	**p=0.005**
Daytime HR[2]	67 (55 – 89)	76 (64 – 101)	**p < 0.001**	**Daytime HR**[2]	69 (65 – 86)	72 (66 – 89)	**p=0.01**
Nighttime HR[1]	64 ± 8	76± 11	**p < 0.001**	**Nighttime HR**[1]	64 ± 6	71 ± 10	**p=0.008**

1 mean ± standard deviation, 2 median with interquartile range (IQR)
HR, heart rate, bpm, beats per minute

DISCUSSION

We found that that severity of renal function impairment in diabetic kidney disease modifies the liraglutide-induced changes of blood pressure, vascular resistance, cardiac hemodynamics and autonomic nervous system activity.

The choice of liraglutide for our study was substantiated by its favorable pharmacokinetic profile in patients with impaired kidney function and large and growing clinical experience with its use in this population (27). Liraglutide is an acylated glucagon-like peptide-1 analogue with prolonged action (28). The pharmacokinetic properties of liraglutide enable 24-h exposure coverage with a Tmax around 10 – 11 hours (26). Liraglutide is not excreted by the kidneys, and is completely degraded to small peptides within the body and renal dysfunction was found not to significantly modify its pharmacokinetic profile (29). In the *post-hoc* analysis of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, this drug had a similar safety profile in patients with and without CKD defined as eGFR < 60 versus ≥ 60 ml/min per 1.73 m^2, respectively (30).

The GLP-1RA liraglutide (31-33), dulaglutide (34) and semaglutide (32) have shown to improve glycemic control in patients with diabetes and very low eGFR, including dialysis patients for liraglutide (35). Although few data are available concerning potential impact of GLP-1R agonists on function of cardiovascular system in patients with impaired kidney function.

In contrast to blood-pressure lowering effect of liraglutide reported in earlier studies (16), our study showed that both systolic and diastolic blood pressure did not decrease in patients with eGFR > 60 ml/min/1.73 m^2. In the patients with advanced CKD, i.e. with eGFR < 30 ml/min/1.73m^2 a single injection of liraglutide led to a significant however only a transient increase of blood pressure. In the LIRA-RENAL study conducted to provide efficacy and safety data in a population with moderate renal impairment (stage 3 CKD), SBP reduction occurred in both treatment groups (–2.45 mmHg with liraglutide; –0.33 mmHg with placebo), but there was no difference between treatments (p = 0.25). There was also no difference between treatments in DBP (p = 0.89) (33).

In our study we were also able to reveal a significant increase of heart rate after liraglutide injection regardless of a degree of renal function impairment. It the LIRA-RENAL trial the mean pulse also increased more with liraglutide (3.20 bpm) than with placebo (0.23 bpm) (2.98 bpm, 95% CI 0.71 – 5.24, p = 0.010) (33).

No single mechanism has been established that may explain a heart rate increase after GLP-1R agonist. It was postulated that the initial increase of heart rate after GLP-1R agonist could be a compensatory mechanism to a decrease of blood pressure caused by both vasodilation and increased natriuresis (36). This

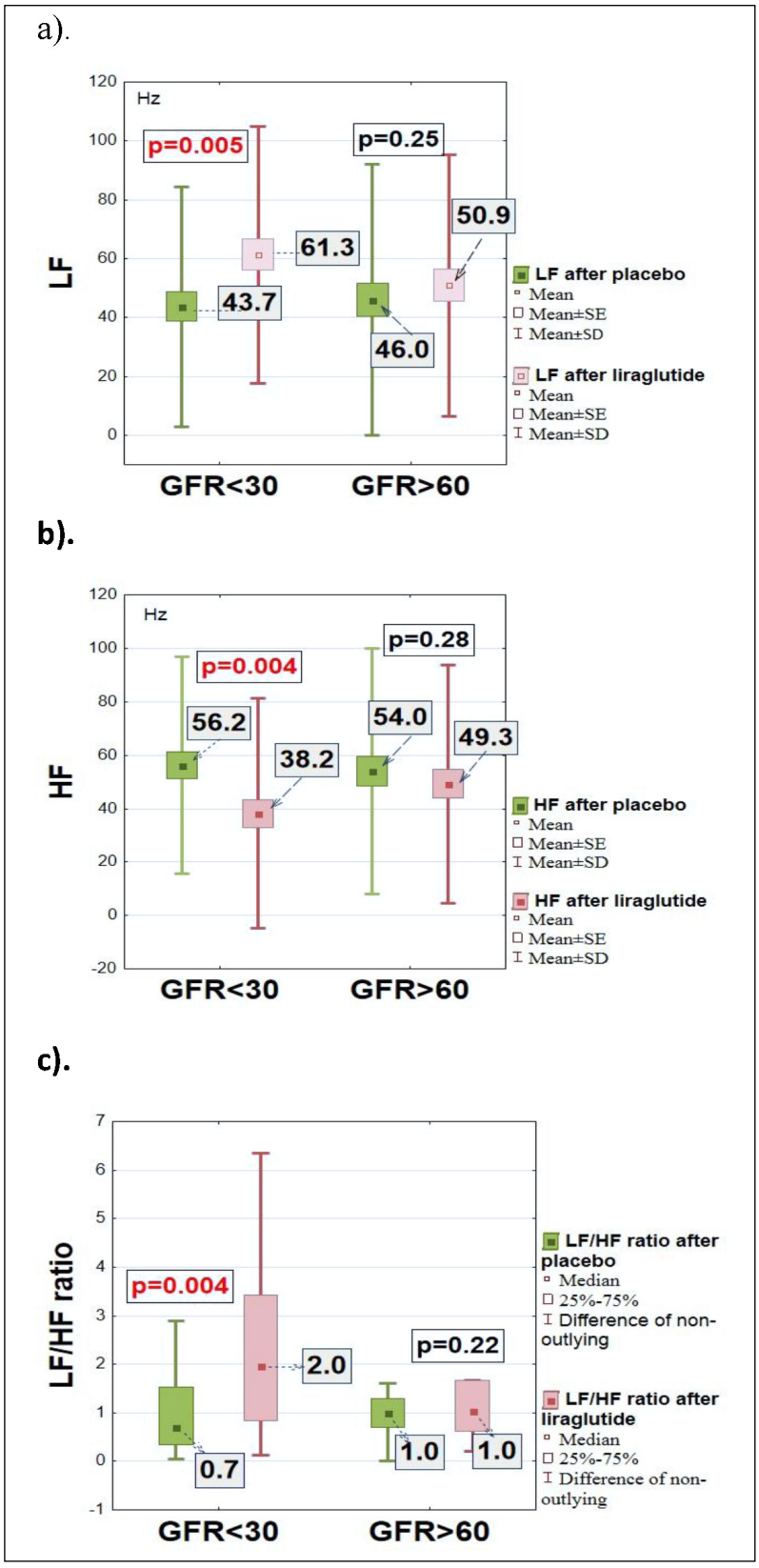

Fig. 3. Effect of liraglutide and placebo on the autonomic nervous system in patients with estimated glomerular filtration rate (eGFR) > 60 and < 30 ml/min/1.73m^2. (a): Low frequencies (LF); (b): High frequencies (HF); (c): LF/HF ratio.

hypothesis has not been however, confirmed by clinical trials (37). Our study showed that in the patients with eGFR < 30 ml/min/1.73 m^2 a significant increase of heart rate seen was accompanied by a simultaneous increase of systolic and diastolic blood pressure. The increase of heart rate was also seen despite a lack of any change of systemic vascular resistance in this group. In the patients with eGFR > 60 ml/min/1.73 m^2 heart rate increased after GLP-1 agonist despite a lack of a significant change of blood pressure, but with significant vasodilation. Similar findings were reported by Mendis *et al*. after a single

Table 4. The changes of the hemodynamic parameters from baseline after a single dose of liraglutide or placebo in patients with eGFR > 60 and < 30 ml/min/1.73m^2.

Change of parameter after intervention (Δ)[1]	**eGFR < 30 ml/min/1.73m^2**			**eGFR > 60 ml/min/1.73m^2**		
	Placebo	**Liraglutide**	**p** (liraglutide vs. placebo)	**Placebo**	**Liraglutide**	**p** (liraglutide vs. placebo)
Δ SV	0.5 (–2.3) – (3.4)	1.8 (–4.2) – (7.8)	0.4	–0.2 (–3.2) – (2.8)	0.2 (–4.9) – (5.2)	0.9
Δ CO	0.1 (–0.1) – (0.4)	0.7 (0.3) – (1.1)	**0.006**	–0.02 (–0.2) – (0.2)	0.4 (0.1) – (0.7)	**0.01**
Δ CI	0.1 (–0.04) – (0.2)	0.3 (–0.1) – (0.5)	**0.006**	0.02 (–0.1) – (0.1)	0.2 (0.04) – (0.4)	**0.01**
Δ EF	0.7 (–1.9) – (3.2)	3.3 (–2.3) – (8.9)	0.3	–0.2 (–1.2) – (0.8)	1.7 (–1.3) – (4.8)	0.1
Δ LVET	10 (–9.9) – (29.9)	11.1 (–14.4) – (36.6)	0.9	–7.7 (–36) – (20.7)	–3.6 (–46.4) – (39.3)	0.7
Δ CTI	3.5 (–4.4) – (11.3)	10 (–5.1) – (25.2)	0.3	–1.7 (–6.4) – (3.0)	4.2 (–6.8) – (15.2)	0.3
Δ EDV	2.4 (–18.9) – (23.6)	–7.7 (–30.4) – (15.1)	0.2	–0.3 (–5.7) – (5.3)	–6.5 (–15.8) – (2.8)	0.3
Δ LCWi	0.2 (–0.03) – (0.4)	0.5 (0.2) – (0.8)	0.06	0.01 (–0.2) – (0.2)	0.4 (0.1) – (0.6)	**0.01**
Δ TFI	–0.4 (–3) – (2.2)	–5.2 (–10) – (–0.4)	**0.01**	1.1 (–0.9) – (3.0)	0.2 (–8.9) – (9.2)	0.5
ΔEDFR	–3.6 (–6) – (–1.1)	5.7 (–2.6) – (13.9)	**0.03**	1.9 (–1) – (4.9)	4.3 (–3.5) – (12.1)	0.3

1 mean, 95% confidence interval, 2 median, 95% confidence interval
SV, stroke volume; CO, cardiac output; CI, cardiac index; EF, ejection fraction; LVET, left ventricular ejection time; CTI, contractility index; EDV, early diastolic volume; LCWi, left cardiac work index; TFI, total fluid index; EDFR, early diastolic filling ratio

Table 5. The change of systemic vascular resistance from baseline after liraglutide and placebo in patients with eGFR > 60 and < 30 ml/min/1.73m^2.

Study group	**Change of parameter after intervention (Δ)**	**Δ SVR**	**Δ SVRI**
eGFR < 30 ml/min/1.73m^2	**Δ effect of placebo**[1]	–33.8 (–64) – (49.6)	–74.2 (–125.1) – (91.8)
	Δ effect of liraglutide[1]	–164.2 (–582.5) – (96.4)	–274.7 (–1170.5) – (239.7)
	p value	0.16	0.09
eGFR > 60 ml/min/1.73m^2	**Δ effect of placebo**[1]	–7.97 (–96.2) – (91.4)	–14.3 (–230.6) – (162.4)
	Δ effect of liraglutide[1]	–147.4 (–338.3) – (152)	–287 (–669.2) – (263.4)
	p value	0.02	0.009

1 mean, 95% confidence interval 2 median, 95% confidence interval
SVR, systemic vascular resistance, SVRI, systemic vascular resistance index

intravenous dose of another GLP-1 agonist exenatide in healthy male subjects (36). In that study heart rate had increased already before the vasodilatory effect was observed, that suggested that these two effects may be independent. Smits *et al*. (38) administrated a combination of exenatide and nitric oxide synthase inhibitor L-N(G) -monomethyl arginine (L-NMMA) to ten healthy men with a simultaneous automated oscillometric blood pressure recordings, finger photoplethysmography and the analysis of heart rate variability. They found that the increases of HR, SBP and sympathetic activity seen in such settings were not accompanied by any changes in total peripheral resistance. That may not confirm the concept of GLP-1RA-induced reflex tachycardia occurring as a response to vasodilation. The effect appears to be mediated by the changes of the sympathetic nervous system activity. Since GLP-1 receptors are present in the sinoatrial node (39) both a direct stimulation of GLP-1

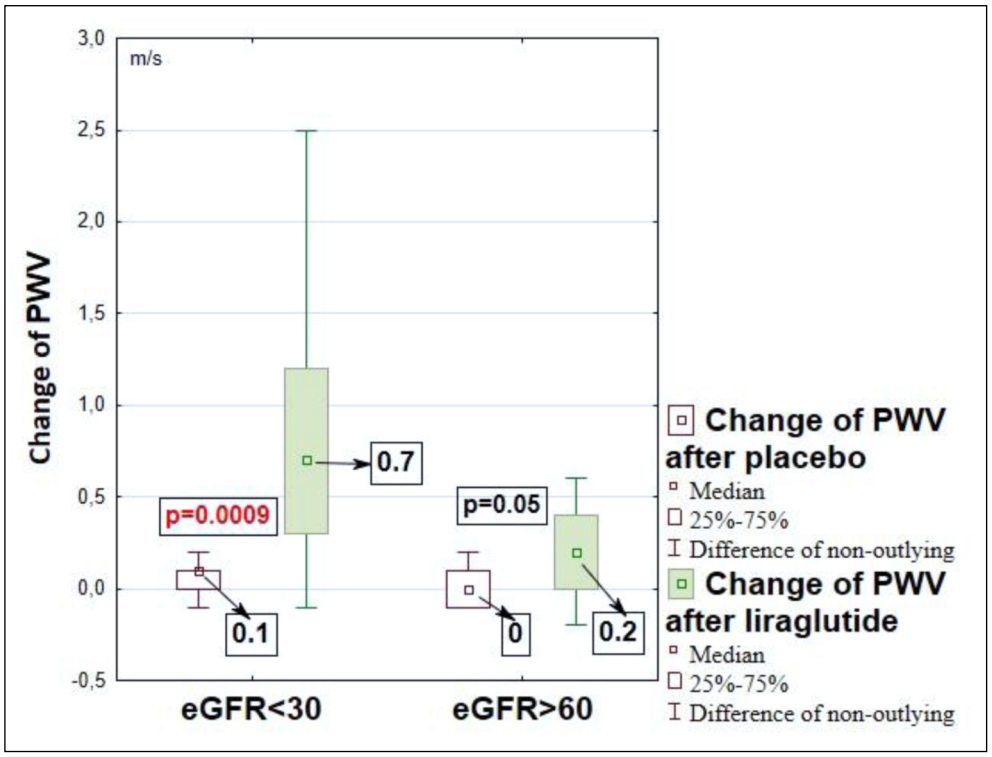

Fig. 4. Pulse wave velocity (PWV) after liraglutide and placebo in patients with estimated glomerular filtration rate (eGFR) > 60 and < 30 ml/min/1.73m^2.

receptors in the conducting system of the heart and an indirect effect mediated by the modulation of autonomic nervous system could explain a positive chronotropic effect of GLP-1R agonist. The results of clinical studies have been inconsistent. In our study a sympathetic activation was seen but was limited to the patients with eGFR < 30 ml/min/1.73 m^2. In study of Bharucha *et al*. muscle sympathetic nerve activity increased after GLP-1 agonist but no simultaneous changes of either cardiac sympathetic or parasympathetic activity were seen (20). Kumarathurai *et al*. studied the effect of liraglutide on the heart rate variability in overweight patients with coronary arteries disease (CAD) and newly diagnosed type 2 *diabetes mellitus* (40). They found that liraglutide administration led to the increase of HR and the reduction of HF power. Such effects were also seen in our study in patients with advanced CKD and these changes were accompanied by a change of LF/HF ratio. We may speculate that disparate effects of GLP-1R agonists on the autonomic nervous system balance might be explained by the use of different GLP-1R agonists, different methods of autonomic system balance assessment and different length of treatment and clinical characteristics of the patients. Liraglutide may increase heart rate through the persistent, relative sympathetic enhancement (41). Therefore heart rate may increase more during the night when the parasympathetic activity predominates. The changes of autonomic nervous system may have been augmented in our study since HRV analysis was performed in the evening, in the time of parasympathetic predominance (42).

In our study the liraglutide-induced change of autonomic nervous system balance was larger in patients with eGFR < 30 ml/min/1.73 m^2 most probably due to a higher baseline activity of sympathetic nervous system that is typically seen in CKD (24).

In studies performed in healthy volunteers Smits *et al*. (38) and Mendis *et al*. (36) revealed a significant vasodilatory effect of GLP-1R agonist. Another study of Smits *et al*. (43) however did not confirm that effect. In our study we found a significant decrease of systemic vascular resistance only in the patients with eGFR > 60 ml/min/1.73 m^2. The natural history of CKD is linked to progressing endothelial dysfunction and arterial calcification that could explain a diminished vasodilatory effect of liraglutide seen in our study in the group with eGFR < 30 ml/min/1.73 m^2.

In our study a significant increase of pulse wave velocity was only noted in patients with advanced CKD. We may speculate that this change could have been caused by simultaneous increase of blood pressure, heart rate, systemic vascular resistance and sympathetic activity observed after liraglutide. The results of our study were similar to those seen in a study of Tonnejick *et al*. in patients with type 2 diabetes mellitus (44). The chronic treatment with GLP-1R agonists improved metabolic parameters and body mass with the accompanying decrease of blood pressure (45, 46). All these changes could affect pulse wave velocity. The results of the study of Lambadiari *et al*. (47) may also corroborate these findings. After a 6-month treatment with liraglutide in patients with newly diagnosed type 2 diabetes mellitus a reduced PWV and systolic blood pressure, aortic blood pressure and augmentation index were seen. Our study assessed only an acute hemodynamic effect of liraglutide and we did not see any significant changes of central aortic pressure. The decrease of the absolute value of augmentation index seen in patients with eGFR < 30 ml/min/1.73 m^2 after liraglutide was probably result of the simultaneous heart rate increase since no significant change of augmentation index corrected for heart rate value 75/min was seen.

In both our groups significant increases of cardiac output were noted without any significant changes of stroke volume. Therefore increased cardiac output after liraglutide could result from increased heart rate. The similar simultaneous increase of heart rate and cardiac output was reported by Asmar *et al*. (48) and Bremholm *et al*. (49). The increase of heart rate in our study was associated with increase of left ventricular cardiac work index an equivalent of myocardial oxygen demand (50). The similar observation was made by Smits *et al*. after the injection of exenatide to healthy volunteers (38) who noted a

significant increase of rate-pressure product 90 minutes after a dose of exenatide.

Additionally a significant decrease of subendocardial viability ratio assessed by the applanation tonometry in our study may suggest that liraglutide may also impair the coronary flow reserve in diabetic kidney disease. The similar decrease of SEVR value was reported by Smits *et al*. in patients with type 2 diabetes mellitus (43). The increase of heart rate seen in our study may have caused significant decrease of SEVR values seen in both groups. GLP-1R agonist have been shown to increase myocardial glucose uptake (51), that may be protective in context of increase of myocardial oxygen demand and impaired coronary flow reserve after GLP-1R agonists treatment. That effect appears to be transient since after the 12-week treatment with exenatide no significant change of SEVR was detectable (43).

The other group of hypoglycemic agents with proven cardioprotective effect is SGLT2 inhibitors. In most trials with SGLT-2 inhibitors, a reduction in systolic BP in the magnitude of 3 – 5 mmHg and diastolic BP of 2 mmHg has been documented (52). Contrary to our findings, this has been observed without a compensatory increase in heart rate. Dedicated 24-h ambulatory BP measurement studies have confirmed these data (53). The reason for the observed BP reduction with SGLT-2 inhibitors involves several pathways including a modest diuretic effect (54), weight reduction and potentially some sodium depletion (55). Interestingly, data from an 8-week mechanistic trial demonstrated that empagliflozin reduced arterial stiffness in patients with type 1 *diabetes mellitus* (56) thus, a direct vascular effect might also contribute the blood pressure changes. The findings of no increased heart rate in the setting of BP reduction may be interpreted as a result of relative reduction in the sympathetic nervous system tone, although modulation of other neurohormonal factors also could play a role (56). The effects of canagliflozin on cardiovascular and renal outcomes were not modified by baseline level of kidney function in people with type 2 diabetes down to eGFR levels of 30 mL/min/1.73 m^2 (57). Effects of empagliflozin on these outcomes were also consistent across categories of eGFR from level 30 mL/min/1.73 m^2 to 60 mL/min/1.73 m^2 (58). Additionally according to the previous metanalyses SGLT2 inhibitors significantly decreased the risk of primary cardiovascular outcomes throughout the spectrum of different kidney functions, including stage 4 (59, 60). Pre-clinical study e.g. showed that empagliflozin administration in prediabetic rats has an important systemic metabolic effect on alterations in substrate utilization, diverting from glucose oxidation to fatty acid oxidation and increasing ketone body use. Improved oxidative and dicarbonyl stress and decreased uric acid seem to play an important role in the cardio- and reno-protective effects of SGLT-2 inhibitors (61). Therefore they may be consider as more appropriate therapeutic option for patients with advanced diabetic kidney disease within the context of findings regarding liraglutide in our study, but this area requires further exploration.

Our study has limitations such as small sample size and evaluation of only acute effect, lack of assessment of liraglutide blood concentration, and recruitment of patients with only two stages of chronic kidney disease. Despite that we were able to show that the hemodynamic effect of liraglutide is dependent on kidney function. Liraglutide administration in patients with advanced chronic kidney disease causes a transient increase of systemic blood pressure secondary to the increased cardiac output. The increased cardiac output in turn depends on increased heart rate associated with a sympathetic predominance. The vasodilatory effect of liraglutide seems to wane in more advanced chronic kidney disease.

Conflict of interest: None declared.

REFERENCES

1. Mrozikiewicz-Rakowska B, Maroszek P, Nehring P, *et al*. Genetic and environmental predictors of chronic kidney disease in patients with type 2 diabetes and diabetic foot ulcer: a pilot study. *J Physiol Pharmacol* 2015; 66: 751-761.
2. Aladaileh SH, Al-Swailmi FK, Abukhalil MH, Shalayel MH. Galangin protects against oxidative damage and attenuates inflammation and apoptosis via modulation of NF-κB p65 and caspase-3 signaling molecules in a rat model of diabetic nephropathy. *J Physiol Pharmacol* 2021; 72: 35-44.
3. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol* 2012; 8: 728-742.
4. Bethel MA, Patel RA, Merrill P, *et al*. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol* 2018; 6: 105-113.
5. Sattar N, Lee MM, Kristensen SL, *et al*. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol* 2021; 9: 653-662.
6. Gerstein HC, Sattar N, Rosenstock J, *et al*. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. *N Engl J Med* 2021; 385: 896-907.
7. Lawes CM, Vander Hoorn S, Rodgers A, *et al*. Global burden of blood-pressure-related disease, 2001. *Lancet* 2008; 371: 1513-1518.
8. Goud A, Zhong J, Peters M, Brook RD, Rajagopalan S. GLP-1 agonists and blood pressure: a review of the evidence. *Curr Hypertens Rep* 2016; 18: 16. doi: 10.1007/s11906-015-0621-6
9. Ravassa S, Zudaire A, Diez J. GLP-1 and cardioprotection: from bench to bedside. *Cardiovasc Res* 2012; 94: 316-323.
10. Richter G, Feddersen O, Wagner U, Barth P, Goke R, Goke B. GLP-1 stimulates secretion of macromolecules from airways and relaxes pulmonary artery. *Am J Physiol* 1993; 265: L374-L381.
11. Yu M, Moreno C, Hoagland KM, *et al*. Antihypertensive effect of glucagon-like peptide 1 in Dahl salt-sensitive rats. *J Hypertens* 2003; 21: 1125-1135.
12. Basu A, Charkoudian N, Schrage W, Rizza RA, Basu R, Joyner MJ. Beneficial effects of GLP-1 on endothelial function in humans: dampening by glyburide but not by glimepiride. *Am J Physiol Endocrinol Metab* 2007; 293: E1289-E1295.
13. Nystrom T, Gutniak MK, Zhang Q, *et al*. Effects of glucagon-like peptide-1 on endothelial function in type 2 diabetes patients with stable coronary artery disease. *Am J Physiol Endocrinol Metab* 2004; 287: E1209-E1215.
14. Gutzwiller JP, Tschopp S, Bock A, *et al*. Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin-resistant obese men. *J Clin Endocrinol Metab* 2004; 89: 3055-3061.
15. Gutzwiller JP, Hruz P, Huber AR, *et al*. Glucagon-like peptide-1 is involved in sodium and water homeostasis in humans. *Digestion* 2006; 73: 142-150.
16. Sun F, Wu S, Guo S, *et al*. Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetes Res Clin Pract* 2015; 110: 26-37.
17. Wang B, Zhong J, Lin H, *et al*. Blood pressure-lowering effects of GLP-1 receptor agonists exenatide and liraglutide: a meta-analysis of clinical trials. *Diabetes Obes Metab* 2013; 15: 737-749.

18. Katout M, Zhu H, Rutsky J, *et al*. Effect of GLP-1 mimetics on blood pressure and relationship to weight loss and glycemia lowering: results of a systematic meta-analysis and meta-regression. *Am J Hypertens* 2014; 27: 130-139.
19. Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet* 1999; 353: 617-622.
20. Bharucha AE, Charkoudian N, Andrews CN, *et al*. Effects of glucagon-like peptide-1, yohimbine, and nitrergic modulation on sympathetic and parasympathetic activity in humans. *Am J Physiol Regul Integr Comp Physiol* 2008; 295: R874-R880.
21. Smilowitz NR, Donnino R, Schwartzbard A. Glucagon-like peptide-1 receptor agonists for diabetes mellitus: a role in cardiovascular disease. *Circulation* 2014; 129: 2305-2312.
22. Grassi G, Bertoli S, Seravalle G. Sympathetic nervous system: role in hypertension and in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2012; 21: 46-51.
23. Martens CR, Edwards DG. Peripheral vascular dysfunction in chronic kidney disease. *Cardiol Res Pract* 2011; 2011: 267257. doi: 10.4061/2011/267257
24. Ewen S, Ukena C, Linz D, Schmieder RE, Bohm M, Mahfoud F. The sympathetic nervous system in chronic kidney disease. *Curr Hypertens Rep* 2013; 15: 370-376.
25. Desir GV. Renalase deficiency in chronic kidney disease, and its contribution to hypertension and cardiovascular disease. *Curr Opin Nephrol Hypertens* 2008; 17: 181-185.
26. Jacobsen LV, Flint A, Olsen AK, Ingwersen SH. Liraglutide in type 2 diabetes mellitus: clinical pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 2016; 55: 657-672.
27. Niezen S, Diaz Del Castillo H, Mendez Castaner LA, Fornoni A. Safety and efficacy of antihyperglycaemic agents in diabetic kidney disease. *Endocrinol Diabetes Metab* 2019; 2 :e00072. doi: 10.1002/edm2.72
28. Grossman S. Differentiating incretin therapies based on structure, activity, and metabolism: focus on liraglutide. *Pharmacotherapy* 2009; 29: 25S-32S.
29. Jacobsen LV, Hindsberger C, Robson R, Zdravkovic M. Effect of renal impairment on the pharmacokinetics of the GLP-1 analogue liraglutide. *Br J Clin Pharmacol* 2009; 68: 898-905.
30. Mann JF, Fonseca VA, Poulter NR, *et al*. Safety of liraglutide in type 2 diabetes and chronic kidney disease. *Clin J Am Soc Nephrol* 2020; 15: 465-473.
31. Mann JFE, Orsted DD, Buse JB. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017; 377: 2197-2198.
32. Mosenzon O, Blicher TM, Rosenlund S, *et al*. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. *Lancet Diabetes Endocrinol* 2019; 7: 515-527.
33. Davies MJ, Bain SC, Atkin SL, *et al*. Efficacy and safety of liraglutide versus placebo as add-on to glucose-lowering therapy in patients with type 2 diabetes and moderate renal impairment (LIRA-RENAL): a randomized clinical trial. *Diabetes Care* 2016; 39: 222-230.
34. Gerstein HC, Colhoun HM, Dagenais GR, *et al*. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019; 394: 121-130.
35. Idorn T, Knop FK, Jorgensen MB, *et al*. Safety and efficacy of liraglutide in patients with type 2 diabetes and end-stage renal disease: an investigator-initiated, placebo-controlled, double-blind, parallel-group, randomized trial. *Diabetes Care* 2016; 39: 206-213.
36. Mendis B, Simpson E, MacDonald I, Mansell P. Investigation of the haemodynamic effects of exenatide in healthy male subjects. *Br J Clin Pharmacol* 2012; 74: 437-444.
37. Meier JJ, Rosenstock J, Hincelin-Mery A, *et al*. Contrasting effects of lixisenatide and liraglutide on postprandial glycemic control, gastric emptying, and safety parameters in patients with type 2 diabetes on optimized insulin glargine with or without metformin: a randomized, open-label trial. *Diabetes Care* 2015; 38: 1263-1273.
38. Smits MM, Muskiet MH, Tonneijck L, *et al*. Exenatide acutely increases heart rate in parallel with augmented sympathetic nervous system activation in healthy overweight males. *Br J Clin Pharmacol* 2016; 81: 613-620.
39. Pyke C, Heller RS, Kirk RK, *et al*. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology* 2014; 155: 1280-1290.
40. Kumarathurai P, Anholm C, Larsen BS, *et al*. Effects of liraglutide on heart rate and heart rate variability: a randomized, double-blind, placebo-controlled crossover study. *Diabetes Care* 2017; 40: 117-124.
41. Lorenz M, Lawson F, Owens D, *et al*. Differential effects of glucagon-like peptide-1 receptor agonists on heart rate. *Cardiovasc Diabetol* 2017; 16: 6. doi: 10.1186/s12933-016-0490-6
42. Benarroch EE. Physiology and pathophysiology of the autonomic nervous system. *Continuum* (*Minneap Minn*) 2020; 26: 12-24.
43. Smits MM, Tonneijck L, Muskiet MH, *et al*. Heart rate acceleration with GLP-1 receptor agonists in type 2 diabetes patients: an acute and 12-week randomised, double-blind, placebo-controlled trial. *Eur J Endocrinol* 2017; 176: 77-86.
44. Tonneijck L, Muskiet MHA, Twisk JW, *et al*. Lixisenatide versus insulin glulisine on fasting and postbreakfast systemic hemodynamics in type 2 diabetes mellitus patients. *Hypertension* 2018; 72: 314-322.
45. Scalzo RL, Moreau KL, Ozemek C, *et al*. Exenatide improves diastolic function and attenuates arterial stiffness but does not alter exercise capacity in individuals with type 2 diabetes. *J Diabetes Complications* 2017; 31: 449-455.
46. Hong JY, Park KY, Kim BJ, Hwang WM, Kim DH, Lim DM. Effects of short-term exenatide treatment on regional fat distribution, glycated hemoglobin levels, and aortic pulse wave velocity of obese type 2 diabetes mellitus patients. *Endocrinol Metab* (*Seoul*) 2016; 31: 80-85.
47. Lambadiari V, Pavlidis G, Kousathana F, *et al*. Effects of 6-month treatment with the glucagon like peptide-1 analogue liraglutide on arterial stiffness, left ventricular myocardial deformation and oxidative stress in subjects with newly diagnosed type 2 diabetes. *Cardiovasc Diabetol* 2018; 17: 8. doi: 10.1186/s12933-017-0646-z
48. Asmar A, Simonsen L, Asmar M, *et al*. Renal extraction and acute effects of glucagon-like peptide-1 on central and renal hemodynamics in healthy men. *Am J Physiol Endocrinol Metab* 2015; 308: E641-E649.
49. Bremholm L, Andersen UB, Hornum M, *et al*. Acute effects of glucagon-like peptide-1, GLP-1. *Physiol Rep* 2017; 5: e13102. doi: 10.14814/phy2.13102
50. Jakovljevic DG, Donovan G, Nunan D, *et al*. The effect of aerobic versus resistance exercise training on peak cardiac power output and physical functional capacity in patients with chronic heart failure. *Int J Cardiol* 2010; 145: 526-528.
51. Sulistio M, Carothers C, Mangat M, Lujan M, Oliveros R, Chilton R. GLP-1 agonist-based therapies: an emerging new class of antidiabetic drug with potential cardioprotective effects. *Curr Atheroscler Rep* 2009; 11: 93-99.

52. Mazidi M, Rezaie P, Gao HK, Kengne AP. Effect of sodium-glucose co-transport-2 inhibitors on blood pressure in people with type 2 diabetes mellitus: a systematic review and meta-analysis of 43 randomized control trials with 22 528 patients. *J Am Heart Assoc* 2017; 6: e004007. doi: 10.1161/JAHA.116.004007
53. Scheen AJ. Effects of reducing blood pressure on cardiovascular outcomes and mortality in patients with type 2 diabetes: Focus on SGLT2 inhibitors and EMPA-REG OUTCOME. *Diabetes Res Clin Pract* 2016; 121: 204-214.
54. Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab* 2013; 15: 853-862.
55. Vasilakou D, Karagiannis T, Athanasiadou E, *et al*. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2013; 159: 262-274.
56. Cherney DZ, Perkins BA, Soleymanlou N, *et al*. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. *Cardiovasc Diabetol* 2014; 13: 28. doi: 10.1186/1475-2840-13-28
57. Neuen BL, Ohkuma T, Neal B, *et al*. Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function. *Circulation* 2018; 138: 1537-1550.
58. Wanner C, Lachin JM, Inzucchi SE, *et al*. Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. *Circulation* 2018; 137: 119-129.
59. Li N, Zhou G, Zheng Y, *et al*. Effects of SGLT2 inhibitors on cardiovascular outcomes in patients with stage 3/4 CKD: a meta-analysis. *PLoS One* 2022; 17: e0261986. doi: 10.1371/journal.pone.0261986
60. Cao H, Liu Y, Tian Z, *et al*. Sodium-glucose cotransporter 2 inhibitors benefit to kidney and cardiovascular outcomes for patients with type 2 diabetes mellitus and chronic kidney disease 3b-4: a systematic review and meta-analysis of randomized clinical trials. *Diabetes Res Clin Pract* 2021; 180: 109033. doi: 10.1016/j.diabres.2021.109033
61. Huttl M, Markova I, Miklankova D, *et al*. Metabolic cardio- and reno-protective effects of empagliflozin in a prediabetic rat model. *J Physiol Pharmacol* 2020; 71: 635-645.

Received: September 17, 2021
Accepted: October 30, 2021

Author's address: Prof. Michal Nowicki, Department of Nephrology, Hypertension and Kidney Transplantation, Central University Hospital, Medical University of Lodz, 251 Pomorska Street, 92-213 Lodz, Poland.
E-mail: nefro@wp.pl